JONATHAN L. BENUMOF, MD
CONSULTING EDITOR

Cuk-H02409-17-P02465

ANESTHESIOLOGY CLINICS OF NORTH AMERICA

⑰

Current Concepts in Acute Pain Control

ALAN N. SANDLER, MB, ChB, GUEST EDITOR

VOLUME 10 • NUMBER 2 • JUNE 1992

W. B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
PHILADELPHIA LONDON TORONTO MONTREAL SYDNEY TOKYO

W. B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.

The Curtis Center
Independence Square West
Philadelphia, PA 19106-3399

P24625

The *Anesthesiology Clinics of North America* is also published in translated editions by the following:

Italian	Verduci Editore, Via Gregorio VII 132, 00165 Rome, Italy
Portuguese	Interlivros Edicoes Ltda., Rua Comandante Coelho 1085, 21250 Cordovil, Rio de Janeiro, Brazil
Spanish	Nueva Editorial Interamericana, S. A. de C. V. Cedro 512, Apartado 26370, 06450 Mexico D. F., Mexico

The *Anesthesiology Clinics of North America* is covered in *Current Contents/Clinical Medicine, Excerpta Medica,* and *ISI/BIOMED.*

ANESTHESIOLOGY CLINICS OF NORTH AMERICA **ISSN 0889–8537**
June 1992 **Volume 10, Number 2**

Copyright © 1992 by W. B. Saunders Company. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information retrieval system, without written permission from the publisher. Printed in the United States of America.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by W. B. Saunders Company provided that the base fee of $0.00 per copy plus $0.20 per page, is paid directly to Copyright Clearance Center (CCC), Transactional Reporting Service, 27 Congress St., Salem, MA 01970. Identify this publication by including with your payment the fee code 0889–8537/92 $0.00 + $0.20. For those organizations that have been granted a photocopy license by CCC, a separate system of payment has been arranged. All fees are subject to change without notice.

The *Anesthesiology Clinics of North America* (ISSN 0889–8537) is published quarterly by W. B. Saunders Company. Corporate and Editorial Offices: The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Accounting and Circulation Offices: 6277 Sea Harbor Drive, Orlando, FL 32887-4800. Second class postage paid at Orlando, FL 32887, and additional mailing offices. Subscription price is $69 per year (U.S. student/resident), $78.00 per year (U.S. individuals), $98.00 per year (U.S. institutions), and $104.00 per year (foreign). To receive student and resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Foreign air speed delivery for all *Clinics* is $8.00 per issue. All prices are subject to change without notice. POSTMASTER: Send address changes to the *Anesthesiology Clinics of North America,* W. B. Saunders Company, Periodicals Fulfillment, Orlando, FL 32887-4800.

Customer Service: 1-800-654-2452.

The editor of this publication is Helaine A. Barron, W. B. Saunders Company, The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399.

GUEST EDITOR

ALAN N. SANDLER, MB, ChB, FRCPC, Associate Professor, Department of Anaesthesia, University of Toronto; and Anaesthetist-in-Chief, Department of Anaesthesia, Toronto General Division, The Toronto Hospital, Toronto, Ontario, Canada

CONTRIBUTORS

NEAL H. BADNER, MD, FRCP(C), Assistant Professor, Department of Anesthesiology, University of Western Ontario; and Director, Acute Pain Service, University Hospital, London, Ontario, Canada

TERENCE J. CODERRE, MSc, PhD, Director, Pain Mechanisms Laboratory, Clinical Research Institute of Montreal; Chercheur Adjoint, Département de Médecine, Université de Montréal; and Associate Member, Department of Psychology, McGill University, Montreal, Quebec, Canada

W. THOMAS EDWARDS, PhD, MD; Associate Professor of Anesthesiology, University of Washington-Harborview Medical Center, Seattle, Washington

RICHARD C. ETCHES, MD, FRCP(C), Assistant Professor, Department of Anesthesia, University of Alberta Hospitals, Edmonton, Alberta, Canada

F. MICHAEL FERRANTE, MD, Director, Pain Management Center, Department of Anesthesia, Brigham and Women's Hospital; and Assistant Professor of Anaesthesia, Harvard Medical School, Boston, Massachusetts

L. FODDERIE, MD, Service d'Anesthésiologie de l'Institut Jules Bordet, Brussels, Belgium

JANE M. HENDERSON, MD, FRCPC, Assistant Professor, Department of Anaesthesia, Montreal Children's Hospital and McGill University, Montreal, Quebec, Canada

JOEL KATZ, PhD, MRC Fellow, Department of Psychology, Toronto General Division, The Toronto Hospital; and Assistant Professor, Departments of Behavioral Science and Anesthesia, University of Toronto, Toronto, Ontario, Canada

P. LEBRUN, MD, Laboratoire d'Electrophysiologie, Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium

GRAHAM H. McMORLAND, MB, ChB, DA, FRCPC, Clinical Professor, Division of Obstetric Anaesthesia and Pharmaceutical Sciences, The University of British Columbia; and the Department of Anaesthesia, The Salvation Army Grace Hospital, Vancouver, British Columbia, Canada

RONALD MELZACK, PhD, Professor, Department of Psychology, McGill University, Montreal, Quebec, Canada

ANTHONY L. PANOS, MD, MSc, FRCSC, Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada

LARRY PANOS, MD, FRCPC, Assistant Professor, Director, Acute Pain Service, Department of Anaesthesia, Toronto General Division, The Toronto Hospital, Toronto, Ontario, Canada

ALAN N. SANDLER, MB, ChB, FRCPC, Associate Professor, Department of Anaesthesia, University of Toronto; and Anaesthetist-in-Chief, Department of Anaesthesia, Toronto General Division, The Toronto Hospital, Toronto, Ontario, Canada

M. SOSNOWSKI, MD, PhD, Chef de Clinique Adjoint, Service d'Anesthésiologie de l'Institut Jules Bordet; and Laboratoire d'Electrophysiologie, Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium

MARK S. SHULMAN, MD, Assistant Professor, Department of Anesthesiology, Tufts University School of Medicine; and Department of Anesthesiology, St. Elizabeth's Hospital of Boston, Boston, Massachusetts

DESMOND G. SPENCE, MB, FRCPC, Anaesthetist-in-Chief, Department of Anaesthesia, Montreal Children's Hospital; and Assistant Professor, Department of Anaesthesia, McGill University, Montreal, Quebec, Canada

DONALD S. STEVENS, MD, Assistant Professor of Anesthesiology, University of Massachusetts Medical Center, Worcester, Massachusetts

LORIE WILD, RN, MN, Clinical Nurse Specialist, Acute Pain Management, and Teaching Associate, Department of Anesthesiology, University of Washington Medical Center, Seattle, Washington

CURRENT CONCEPTS IN ACUTE PAIN CONTROL

CONTENTS

Foreword xi
Jonathan L. Benumof

Preface xiii
Alan N. Sandler

Receptors, Neuropathways, and Mechanisms 211
M. Sosnowski, P. Lebrun, and L. Fodderie

To develop new and better treatments for acute pain, we must understand its pathways and mechanisms. This article reviews the different stages of acquisition and processing of nociceptive information from the peripheral nociceptor to the brain. The functioning of different sites and processes that are possible targets for therapeutic intervention are detailed in the light of recent advances in neurochemical and electrophysiologic research.

Measurement of Pain 229
Joel Katz and Ronald Melzack

The most frequently used self-rating instruments for the measurement of pain in clinical and research settings include the visual analogue scale (VAS) and the McGill Pain Questionnaire. The McGill Pain Questionnaire was designed to assess the multidimensional nature of pain experience and has been demonstrated to be a reliable, valid, and consistent measurement tool. A short-form McGill Pain Questionnaire is available for use in specific research settings when the time to obtain information from patients is limited and when more information than simply the intensity of pain is desired. Further development and refinement of pain measurement techniques will lead to increasingly accurate tools with greater predictive powers.

Physiologic Consequences of Tissue Injury and Acute Pain **247**
Terence J. Coderre

This article examines the responses of the peripheral and central nervous systems to noxious stimulation and the prolonged changes in their function that occur after tissue injury or acute pain. Tissue injury leads to pathologic processing of nociceptive information, resulting in reduced pain threshold (allodynia), increased pain sensitivity (hyperalgesia), prolonged responses to brief stimulation (persistent pain), and the spread of pain and hyperalgesia to uninjured tissue (referred pain and hyperalgesia). These pathologic conditions are, in part, mediated by alterations in peripheral nervous system function and are also influenced by alterations in central neural function.

New Techniques of Opioid Administration for the Control of Acute Pain **271**
Alan N. Sandler

Several novel techniques of opioid administration for acute pain control have been developed and explored recently. These include administration through the buccal, nasal, and rectal mucosa, and transdermally. This article examines these techniques in relation to pharmacokinetic profiles, analgesic efficacy, and complications, especially concerning respiratory safety.

Patient-Controlled Analgesia **287**
F. Michael Ferrante

Intravenous patient-controlled analgesia (PCA) with opioids is presently experiencing widespread popularity and growth. The reasons for this are an increased awareness of the inadequacies of traditional opioid regimens in the uniform provision of analgesia, the development of safe infusion technology, and the tremendous patient satisfaction associated with PCA.

New Systemic Analgesic Agents **299**
Mark S. Shulman

Several new systemic analgesics for postoperative pain have been developed. Dezocine, a μ-agonist, is as effective as morphine but may not have the abuse potential or adverse respiratory effects of morphine. Ketorolac, a nonsteroidal anti-inflammatory drug, is a potent pain killer with no abuse potential or serious respiratory or cardiovascular side effects. The α_2-agonists clonidine and dexmedetomidine are useful chiefly to enhance the effects of other analgesic agents. Capsaicin, a topical agent, provides cutaneous analgesia.

Epidural Agents for Postoperative Analgesia 321
Neal H. Badner

This article discusses the current use of intrathecal and epidural agents for the relief of postoperative pain. The application of local anesthetics, narcotics, and α_2-agonists as well as combinations of these drugs is described. Their use is analyzed in terms of efficacy and side effects. Dosing recommendations are given, and areas needing further research are discussed.

Regional and Local Block of Acute Pain 339
Larry Panos and Anthony L. Panos

Regional anesthetic techniques are increasingly used for the management of acute pain. The use of wound infiltration, peripheral nerve, intercostal, interpleural, and major plexus blocks are reviewed. Current experience shows that these techniques are effective and are indicated in selected groups of patients.

Pediatric Acute Pain Control 359
Desmond G. Spence and Jane M. Henderson

It is now generally accepted that even very young children have the capacity to experience pain. The problem remains to find an accurate method of assessing the degree of pain and determining how it is best treated. We continue to learn about how children respond to pain and its treatment as more studies are published. Children should be able to experience a pain-free hospital stay.

Obstetric Pain Management 379
Graham H. McMorland

Obtunding the pain of labor benefits the mother and fetus. The selection of agents and techniques for analgesia must take into account their effects on the mother, fetus, and pattern of labor. The modification of traditional techniques holds the promise of improved analgesia with decreased risk.

Management of Pain in Intensive Care Settings 395
Donald S. Stevens and W. Thomas Edwards

Advanced analgesic techniques are available for use at each level of nociception and pain perception. Interruption or modulation of afferent nerve input can be done in the periphery (nonsteroidal anti-inflammatory drugs, major nerve block, or plexus block), at the spinal cord level (epidural opioids and local anesthetics), or systemically (intravenous opioids by bolus, infusion, or patient-controlled analgesia). Appropriate use of these techniques can significantly improve patient outcome as well as patient comfort.

Complications of Acute Pain Management 417
Richard C. Etches

As techniques of acute pain management become more numerous and more complex so too do complications. Problems common to opioid administration by any route, including nausea, vomiting, pruritus, and urinary retention, are often distressing to the patient but rarely dangerous. Opioid-induced respiratory depression is potentially dangerous and may occur regardless of the route of administration. Causes include drug errors, equipment failure, and an unexpected sensitivity to the drug. To manage acute pain safely and effectively, it is necessary to provide the appropriate education for nurses and physicians and to develop the policies and procedures that will ensure good, safe nursing care.

Nursing Aspects of Acute Pain Management 435
Lori Wild

Acute pain management for patients demands a collaborative effort between physicians, nurses, pharmacists, and other patient-care support departments. Research has shown that collaborative practice among physicians and nurses leads to improved outcomes for patients. The role of the nurse, both at the bedside and within an acute pain service, is expanding and can be a key element of successful pain management for patients. The purpose of this article is to explore and describe the role of nursing in the specialty of pain management.

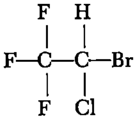
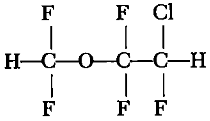
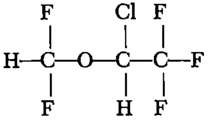
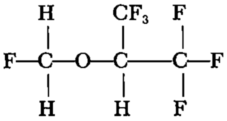
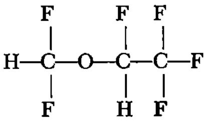
Index 445

Subscription Information **Inside back cover**

ERRATUM

The December 1991 issue of the *Anesthesiology Clinics of North America* contained several errors in Table 1, page 764, in the article "Inhalational Anesthetics in Infants and children," by Jerrold Lerman, MD. The corrected table is printed on page ix of this issue with corrections set in boldface.

Table 1. *Physicochemical Properties of Inhalational Anesthetics*

	HALOTHANE	ENFLURANE	ISOFLURANE	SEVOFLURANE	DESFLURANE
Pharmacology					
Chemical structure					
Molecular weight	197.4	184.5	184.5	200.1	168
Boiling point (°C)	50.2	56.5	48.5	58.6	23.5
Vapor pressure (mm Hg)	244	172	240	185	664
Odor	Mild, pleasant	Etheral	Etheral	Pleasant	Etheral
% Metabolized	**15–25**	**2.4**	**0.2**	**4.5**	**0.02**
Solubility					
$\lambda_{b/g}$ adults	2.4	1.9	1.4	0.66	0.42
$\lambda_{b/g}$ neonates	2.1	1.8	1.2	0.66	—
$\lambda_{fat/b}$ adults	51	—	45	48	27
MAC					
MAC_{adults}	0.75	1.7	1.2	2.05	7.0
$MAC_{neonates}$	0.87	—	1.60	N/A	9.2

Abbreviations: b/g = blood/gas; fat/b = fat/blood.

FORTHCOMING ISSUES

September 1992

CEREBRAL PROTECTION, RESUSCITATION, AND MONITORING:
A LOOK INTO THE FUTURE OF NEUROANESTHESIA
Bruno Bissonnette, MD, *Guest Editor*

The number of recent developments that have improved our ability to monitor, protect, and possibly resuscitate the central nervous system has been enormous and makes neuroanesthesia one of the most active and dominant subspecialities in all of anesthesia. Consequently, this issue of *Anesthesiology Clinics of North America* is most appropriate and timely. The guest editor of this issue, Dr. Bruno Bissonnette, is a world-class neuroanesthetist with outstanding clinical, teaching, and research qualifications; the very modern and up-to-date knowledge of the guest editor guarantees that this issue will be of very high quality and extremely valuable and interesting to all anesthesiologists.

December 1992

EMBOLISM AND ANESTHESIA
Levon M. Capan, MD, and Sanford M. Miller, MD,
Guest Editors

March 1993

NEUROMUSCULAR FUNCTION AND BLOCKADE
Brian L. Partridge, MD, *Guest Editor*

RECENT ISSUES

March 1992

EPIDURAL AND SPINAL ANALGESIA AND ANESTHESIA:
CONTEMPORARY ISSUES
M. S. Batra, MD, *Guest Editor*

December 1991

NEW DEVELOPMENTS IN PEDIATRIC ANESTHESIA
Jerrold Lerman, MD, *Guest Editor*

September 1991

MYOCARDIAL ISCHEMIA AND PERFORMANCE
Peter C. Duke, MD, *Guest Editor*

FOREWORD

The safe control of acute perioperative pain is most often a patient's greatest concern and is often the treating physician's highest priority. Consequently, it is no surprise that research into acute pain control and useful developments stemming from this research have occurred at an extremely rapid pace. The rapid pace of important developments in acute pain control requires that reviews of clinically relevant progress appear every few years to best enable the practicing anesthesiologist to control acute pain. This issue of *Anesthesiology Clinics of North America* covers the entire breadth of important intellectual and practical considerations in acute pain control. The discussions range from basic considerations such as pain receptors, pathways, mechanisms, measurement, physiology, and pathophysiology to the therapy of acute pain in every relevant hospital setting (e.g., intensive care, pediatric, obstetric, and other environments) and from new techniques and drugs to the very important nursing care aspects and the diagnosis and treatment of complications.

Dr. Alan Sandler is eminently qualified to be the guest editor of this issue of *Anesthesiology Clinics* on "Current Concepts in Acute Pain" because of his extensive and internationally recognized clinical, research, and teaching contributions. First and foremost, over the last decade Dr. Sandler has developed a clinical acute pain service and research unit at The Toronto Hospital, which has thrived and flourished in both respects. As a consequence of, and testimony to, the clinical care and research excellence of this service, special fellowship training in the management of acute pain at The Toronto Hospital is highly sought after by physicians desiring expertise in this area. Second, Dr. Sandler is very well funded, and presently, an extremely active and productive researcher in many aspects of acute pain control. He has published extensively in the best peer-reviewed journals on spinal cord trauma, alternative routes of opioid administration for acute pain control including transdermal therapeutic systems and epidural opioids, monitoring techniques of the safety of opioid administration, and physiologic assessment of the up regulation of the spinal cord. For just one example of the depth of his research, Dr. Sandler has been funded and has published separately major studies of epidural morphine, fentanyl, sufentanyl, and nalbuphine for the relief of postthoracotomy pain and after cesarean section. Third, he is a highly credentialed teacher having presented many research papers and lectures at numerous meetings as well as having organized meetings. He now serves as an external reviewer for several journals and funding agencies and is well admired and respected by The

Toronto Hospital Residents and Fellows. This issue of *Anesthesiology Clinics of North America* on "Current Concepts in Acute Pain Control" is an outstanding contribution because of the timeliness and importance of the subject matter, and the credentials and expertise of the guest editor, Dr. Alan Sandler, guarantee the quality of the issue.

JONATHAN L. BENUMOF, MD
Consulting Editor

PREFACE

Interest in all aspects of acute pain control is increasing very rapidly in the 1990s, with anesthesiology playing a decidedly prominent role. Health-care workers now have available publications, workshops, and meetings around the globe devoted to acute and chronic pain control. With this intense scrutiny, it is not surprising that new information from studies relating to basic science, therapeutic modalities, and outcome is appearing virtually on a daily basis. The increasingly diverse techniques available to control acute pain effectively are being examined scientifically to determine which therapies are the most effective for each situation and to document complications and side effects. Much of this impetus has come from the formation of acute pain services, again primarily from anesthesiology departments, which have actively used the new acute pain therapies and provided extensive experience of the pros and cons of each form of treatment. Many of the authors who have contributed articles to this issue of *Anesthesiology Clinics of North America* are directors of acute pain services in their institutions and are thus able to provide us with the benefit of both theoretic and practical experience in the discussions of their topics. The rapid change in experimental knowledge related to pain mechanisms prompted the inclusion of chapters related to receptors, neuropathways, and mechanisms as well as the physiologic consequences of tissue injury. The measurement of pain is also extensively discussed, as it is only by careful measurement of this subjective phenomenon that we will be able to continue to refine our methodology. The rest of the text provides articles relating to current and new pain control techniques as well as an evaluation of pain control in different patient populations. I hope this issue will provide useful information to its readers but more importantly continue to reinforce the leadership role anesthesiology has demonstrated in the understanding and treatment of acute pain conditions.

ALAN N. SANDLER, MB, CHB, FRCPC
Guest Editor

Department of Anaesthesia
Toronto General Hospital
200 Elizabeth Street, GW2-502
Toronto, Ontario
Canada M5G 2C4

RECEPTORS, NEUROPATHWAYS, AND MECHANISMS

M. Sosnowski, MD, PhD, P. Lebrun, MD,
and L. Fodderie, MD

THE ORIGIN OF PAIN

The pain we perceive after a burn, bite, or pinch is readily identifiable but difficult to define because it is differently perceived at different thresholds by different individuals. In the normal human being, the identification of a sensation as being painful is a function of higher associative centers of the brain in response to afferences from the periphery. The term *nociception* is used to describe the neural response to stimuli potentially damaging to the individual. These nociceptive afferences are then interpreted and modulated according to motivational and cognitive factors,[41] such as prior experience, level of attention, anticipation, or suggestion. Acute pain is thus a subjective sensation in response to objectifiable signals, the "psychical adjunct of a protective reflex" described by Sherrington in 1906.[99a] However, before these afferences reach the brain and are recognized as painful, a considerable amount of processing has already taken place, both in the periphery and spinal cord.

The Periphery

Peripheral Receptors

In 1838, Johannes Müller first proposed that the mechanisms subserving the different sensory modalities are distinct, so that the

---

From the Laboratoire d'Electrophysiologie, Faculté de Médecine, Université Libre de Bruxelles, and Service d'Anesthésiologie de l'Institut Jules Bordet, Brussels, Belgium

same stimulus will produce a different sensation if applied to different types of nerves.[101] In 1894, Von Frey postulated the existence of specific receptors for pain projecting to pain centers in the brain, basing this theory on observations by Blix[13] that the stimulation of discrete points on the skin did give rise to different sensations (touch, cold, warmth, or pain), and proposed free nerve endings as the histologic correlate of the nociceptor. However, the theory that pain is caused by the activation of specific receptors, the "doctrine of specific nerve energies" or specificity theory, was disputed by Goldscheider, who proposed that pain arises from excessive activity of any type of receptor by a central summation process. This led to the pattern theory of Nafe,[86] who proposed that pain is signalled by the temporal and spatial patterns of response of nonspecific receptors. However, neither of these two theories has adequately explained the experimental evidence that has been accumulated since the development of electrophysiologic techniques.

Structures potentially capable of encoding nociceptive information are multiple. Two characteristics are necessary for a receptor to be classified as a nociceptor[11]: a threshold higher than that of low-threshold mechanoceptors or thermoceptors, and the ability to encode the intensity of noxious stimuli. In the 1960s, electrophysiologic recordings of single nerve fibers, notably by Perl,[12, 23] permitted the identification of subgroups of afferent fibers having these two characteristics.[60, 63, 115] Low, non-noxious stimulation intensities activate large-diameter (15–20 μm) Aβ and Aα (in muscle) fibers, mediating epicritic sensation (proprioception, light touch, temperature discrimination). Stimulation at noxious intensities activates Aδ (4 μm) and C (0.5 μm, unmyelinated) fibers, together forming the afferent pathway for protopathic (noxious) sensation. The existence of these two major systems of afferent fibers also has been distinguished at the spinal and cerebral levels,[2] but the distinction between epicritic and protopathic systems in the periphery is more functional than morphologic, because conduction velocities of certain nociceptors have been shown to be as high as 50 m/sec in monkeys,[25] indicating a degree of overlap between Aβ and Aδ fibers. The activation by noxious stimuli of two different types of fibers (Aδ and C) could explain the double sensation of pain evoked in humans by a single short noxious stimulus: a rapid (0.1 second latency) pricking pain (first pain) carried by Aδ fibers, with conduction velocities of 5 to 35 m/sec followed approximately 1 second later by a burning pain (second pain) mediated by C fibers (conduction velocity, 0.5–1.4 m/sec).

Single-unit recordings have permitted the identification of certain types of high-threshold receptors responding to specific stimuli. Mechanonociceptors respond almost exclusively to excessive pressure (pinch or prick).[23] These receptors are most often innervated by Aδ fibers. Uniquely heat-,[7] cold-,[85] or chemical-[85] specific receptors do exist, but seem to be rare. Mechanically insensitive afferents, also called "silent nociceptors" or "sleeping afferents," are normally unresponsive to transient excessive stimulation, but become sensitive to mechanical stimuli in the presence of inflammation.[38, 71, 99] However, the most prevalent type of receptors are polymodal, responding to excessive pressure, temperatures above 42°C or below 18°C, and to the presence of algogenic substances. Within this vast population of receptors, several subtypes can be distinguished. Polymodal nociceptors innervated by A fibers are designated *A mechanoheat receptors* and have been further categorized into types I and II, depending on their response to heat stimuli.[26] Type I receptors typically respond to higher temperatures (over 53°C) and have rapid conduction velocities. They are more prevalent on glabrous skin, as opposed to type II receptors, more prevalent in hairy skin. The threshold of activation of type II A mechanoheat receptors is lower, and the latency between stimulus onset and activation is shorter than type I A mechanoheat receptors. This, and the fact that type II receptors have small (1–4 mm^2) receptive fields compared with type I fibers (33–41 mm^2),[96] makes the former more likely to signal first pain. Second pain is signaled by C mechanoheat receptors. Although the perceived level of pain is proportional to the initial discharge rate, their activity has not always paralleled the sensation of pain in human volunteers.[1, 26, 96] The initial response to a high temperature applied to the glabrous skin of the hand rapidly adapts to a low level, while A mechanoheat receptors typically have the reverse response.[96]

This classification is far from being strict. The range of response of these nociceptors is variable as is the nature of the stimuli that activate them. Further confusion is added by the phenomenon of sensitization. There are two categories of sensitization: peripheral sensitization of primary afferents and central sensitization of dorsal horn neurons.

Peripheral Sensitization

The specific nociceptors become responsive to a wider range of stimuli when stimulated repeatedly[54] or in the presence of sustained stimulation of another type,[35, 87] e.g., an Aδ mechanonociceptor can respond like a C mechanoheat receptor after thermal stimuli.[25, 51] Sensitization is marked by several changes: a lower threshold of activation; a shorter response latency; an increase in response to a given stimulus intensity; and the onset of spontaneous activity.[25] This phenomenon is a possible explanation for primary hyperalgesia, the decrease in pain threshold at the site of an injury.[72]

Knowledge of the mechanisms of activation of nociceptors remains limited. Mechanical and thermal receptors are probably activated directly by the stimulus.[15] The activation of polymodal nociceptors is potentiated by a variety of substances (histamine, kinins, serotonin, prostaglandins, leukotrienes, adenosine triphosphate, H^+, K^+, and so forth) that may act as intermediaries.[21, 45, 46, 55, 68, 75, 77] These substances have been shown to potentiate nociceptor response to other algogenic substances, and their presence is associated with the presence of C fibers and inflammation.

The link between C fibers and inflammation is due to the secretory functions of these fibers, not always associated with reflex or sensory effects.[79] In addition to an afferent volley on activation by local injury, peripheral C-fiber terminals release a variety of factors, creating a widening area of neurogenic inflammation.[21, 75, 105] This "axon flare" can equally be evoked by antidromic stimulation intense enough to activate C-fibers[27, 57] and is prevented by pretreatment with capsaicin, a neurotoxin that is selective for neuropeptide-containing small-diameter fibers.

The substance most prevalent in vesicles isolated from terminals of small diameter fibers, both centrally and peripherally, is the neuropeptide substance P. Significantly, the inflammatory effects produced by C-fiber stimulation are replicated by peripheral administration of substance P analogues.[52] Substance P is not the only peptide found in unmyelinated sensory neurons: over a dozen peptides[64] have been found in primary sensory neurons and may contribute to neurogenic inflammation. When natural stimuli activate fine afferents, substance P is probably released locally by an axon reflex; it induces a vasodilation and acts indirectly on nociceptors by eliciting mast cell degranulation, resulting in the release of histamine and serotonin[49, 52, 106] and increased synthesis and release of other unstored mediators of inflammation, such as leukotrienes[112] (Fig. 1).

The effect of this release of proinflammatory agents is to sensitize adjacent nociceptors (secondary hyperalgesia), resulting in an increase in the spontaneous activity of some nociceptors that can produce membrane depolarization of dorsal horn neurons. Under these conditions, inputs at synapses that were ineffective under the normal conditions may be able to generate action potentials after sensitization.

Nevertheless, this "cascade" of peripheral changes in sensitivity is too small to account for all the injury-induced alterations. Consequently, it appears that the inflammation process, together with an increase in afferent barrage, initiates some central changes (central sensitization) (Fig. 2).

Clinical Applications

As originally suggested by Lewis,[78] local application of Xylocaine (lidocaine) will stop the development of secondary hyperalgesia.

As analgesic actions of anti-inflammatory agents (aspirin, indomethacin) are due to their inhibitory effects on prostaglandin synthesis, antiserotoninergic and antihistaminic agents (that will antagonize nociceptors sensitization) may provide a novel approach to the production of new analgesic drugs.

The presence of opioid and α_2-receptors on the terminals of unmyelinated nerves also is of therapeutic importance.[33, 91, 100, 102] The physiologic importance of these receptors is not quite clear at present, but it has been shown that peripherally applied opioids are analgesic[6, 76] only in the presence of inflammation, indicating that they do not directly affect nociceptor function, but are involved in the modulation of processes related to the development of inflammation. The presence of adrenergic receptors on peripheral nociceptors is indicative of the

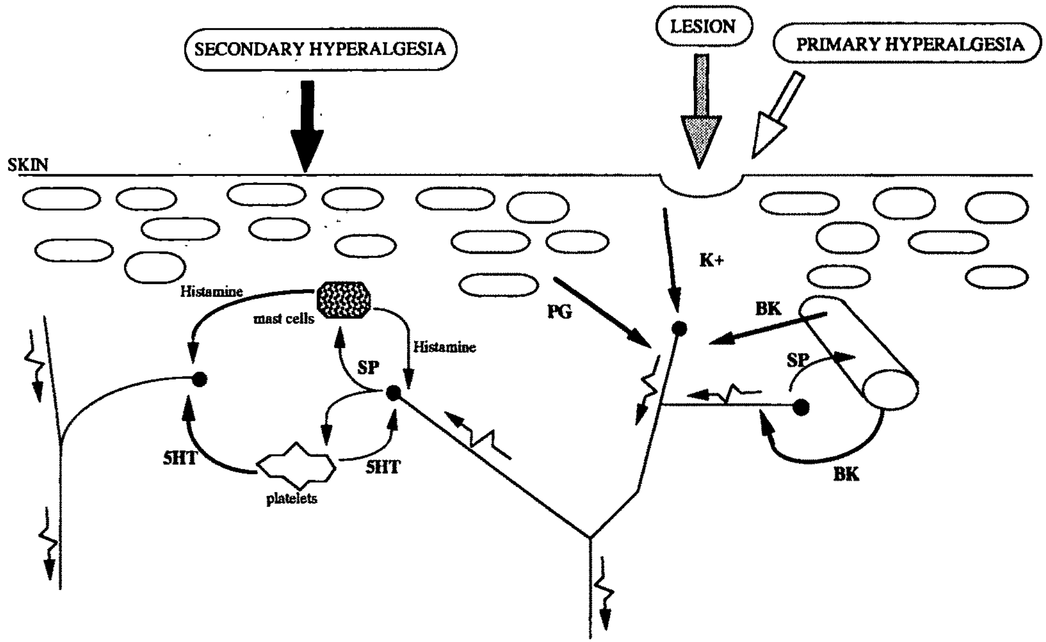


Figure 1. Peripheral sensitization. The biochemicals released by tissue injury (K^+, PG, BK, etc.) excite nociceptors or increase their sensitivity (primary hyperalgesia). Substance P released by an axon reflex induces vasodilatation and mast cell degranulation, resulting in the release of histamine and serotonin. These pro-inflammatory agents will sensitize adjacent nociceptors: the snow-ball phenomenon responsible for the secondary hyperalgesia can start. Abbreviations: K^+ = potassium; PG = prostaglandin; BK = bradykinin; SP = substance P; 5HT = serotonin.

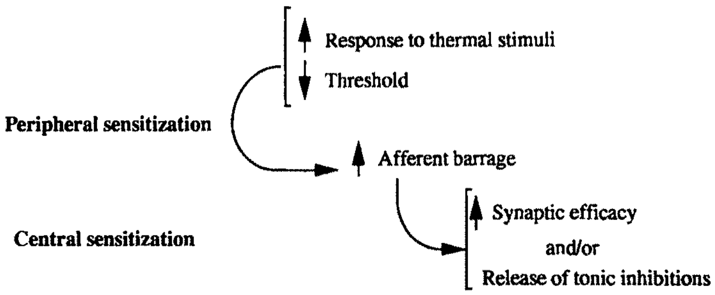


Figure 2. From peripheral injury to central sensitization: cascade of changes.

role of sympathetic innervation on the function of nociceptors. Once again, these are important, not so much in the immediate reaction to a painful stimulus, but in states of enduring or chronic pain.

Noncutaneous Nociceptors

Although most of the studies concerning receptors to noxious stimuli have involved cutaneous nociceptors, pain arising from viscera, joints, or muscles is more commonly encountered in a clinical setting. The existence of specific nociceptors in these structures is now beyond doubt.[22, 69, 70, 107] Pain from muscles and joints is evoked by a variety of mechanical, thermal, or chemical stimuli, such as cutaneous pain, and is mediated by somatic nerves, resulting in a clearly perceived and well-localized sensation. Visceral pain is evoked by smooth muscle spasm, ischemia, inflammation, and other chemical stimuli as well as by mechanical stimuli such as distension or traction of the mesentery. However, burning, cutting, crushing, or other forms of serious injury are often indolent. In addition, visceral nociceptive fibers run in sympathetic and parasympathetic nerves, and the pain evoked by the activation of these fibers often has no precise localization.[28] Thus, the reason for visceral pain is less clear than for cutaneous or articular pain, which activates protective reflexes having undeniable survival value. Pain cannot be evoked from all viscera (e.g., brain), and it is not clear why specific nociceptors are present in certain organs (bile duct, heart, lung, testis) and only nonspecific receptors in others (e.g., colon). In addition, the density of innervation of viscera, especially the gastrointestinal tract, is particularly low and accounts for the generally diffuse and poorly localized nature of abdominal pain. According to Cervero,[30] a population of nonspecific afferent fibers exists with a continuum of thresholds ranging from innocuous to noxious. Pain is evoked by both temporal and spatial summation at the spinal cord level as more and more of these receptors are activated.

The Dorsal Horn

Organization

The cell bodies of primary afferent fibers are located in the dorsal root ganglion and give rise to axons that enter the spinal cord through the dorsal roots. There is evidence for the existence of unmyelinated afferents in the ventral root,[32, 34, 37] a possible explanation for the occasional failure of posterior rhizotomy to relieve intractable pain. The axons are separated into contingents of large- and small-diameter fibers in the dorsal root entry zone, and the Aδ and C fibers then pass into Lissauer's tract, where they may rise or descend as much as three levels before entering the dorsal horn. The cytoarchitecture of the spinal gray matter was first defined by Rexed,[98] who distinguished 10 lamina, the first six making up the dorsal horn. Collaterals from C fibers terminate almost exclusively in laminae I and II, the most peripheral. Lamina II is the substantia gelatinosa, and the dense terminations of both C and Aδ fibers in this zone is one of the reasons why it is considered to be the primary site of nociceptive afferent processing.[82] Aδ fibers terminate both in the most superficial parts of the dorsal horn, laminae I and II, and in lamina V. Electrophysiologic studies have shown that lamina V cells respond to both low- and high-threshold mechanoreceptors. In addition to lamina V, the major terminal area for nonnociceptive afferences is in laminae III and IV. Once these large-diameter fibers reach lamina IV, many give off collaterals that turn back to terminate in laminae II and III.[16]

This pattern for cutaneous afferences is not shared by deeper structures. Nociceptive afferents from muscle[50] (type III and IV fibers) and viscera[43] have been shown to project on lamina I, then on laminae V and VI, with few or no projections in between. Afferences from the gastrointestinal tract are carried almost exclusively by sympathetic nerves[28] to the sympathetic chain, and from there into spinal cord from T1 to L2. Afferences from bladder and genitalia enter the cord via the sacral plexus, at S2 to S4.[50] The vagus nerve contains a large contingent of C fibers from thoracic viscera that have been shown to terminate in the nucleus of the solitary tract[50] in the brain stem. Contrary to cutaneous afferences, muscular, articular, and visceral inputs are not organized somatotopically and are widely distributed up and down the cord. Although the total number of visceral afferents is small (approximately 10% of total afferents), they activate a large number of spinal neurons, indicating extensive divergence.

Two major classes of neurons responding to nociceptive stimuli have been identified in the dorsal horn. Nociceptive-specific neurons have no background activity and do not respond to gentle mechanical or thermal stimuli. These neurons are most abundant in lamina I, where they are organized somatotopically.[95, 114] Their receptive fields are discrete and vary from one to several square centimeters.[94, 114] The effectiveness of a stimulus varies over different parts of the field, the central area being the most sensitive. However, the ability of these cells to encode the intensity of noxious stimulation seems weak.[58] Wide dynamic range (WDR) neurons, also called nociceptive nonspecific, or convergent neurons,[74] receive Aβ-, Aδ-, and C-fiber afferences. They are the most prevalent cells in the dorsal horn and can be found in all laminae, although they are most dense in lamina V. In contrast to cells that respond uniquely to innocuous or nociceptive afferences, these cells respond to a wide range of stimuli in a graded manner, increasing their rate of firing exponentially[66] from gentle touch or low heat to noxious pinch or temperatures over 50°C. Their receptive fields are usually larger than those of nociceptive-specific neurons, varying from the area of a digit for neurons having distal fields to most of a limb for the more proximal. The different parts of the receptive field are again differentially sensitive. The central area is sensitive to both innocuous and noxious stimuli and the peripheral area to noxious stimulation only.[93] In addition, an inhibitory zone adjacent to the primary receptive field has been described.[10, 56, 109, 110] Although nociceptive-specific cells receive some visceral afferents, there is a much larger degree of viscerosomatic convergence on WDR neurons, which may contribute to the phenomenon of referred pain.

The significance of these two populations of nociceptive neurons is not quite clear. The exclusive nature of the input to nociceptive-specific neurons, as well as their small well-localized receptive fields, would indicate a role in the sensory-discriminative aspect of pain sensation. WDR neurons have better intensity coding and a higher degree of convergence, indicating a possible role in causing reflex modulations of a wide variety of bodily functions in reaction to pain by the extraction of certain modalities subserving higher integrative processes. However, the involvement of WDR neurons in sensory-discriminative processing is equally likely and no hard and fast distinction between the functions of the two types of neurons can yet be asserted.

Spinal Afferent Processing

The specificity and pattern theories of pain sensation were reconciled by the gate control theory of Wall and Melzak[82, 111] in 1965. They proposed that ascending dorsal horn neurons (T cells) receive not only peripheral excitatory afferences from small diameter fibers, but also are subject to facilitation or inhibition by other peripheral and supraspinal structures, mediated by cells in the substantia gelatinosa. The transmission of nociception toward the brain is thus a balance between these excitatory and inhibitory influences, and pain results when there is an excess of nociception. It is now well established that activation of large-diameter afferent fibers is capable of inhibiting or suppressing the activity of WDR neurons. These effects are segmental and are localized within the substantia gelatinosa, where the majority of C fibers terminate. Large-diameter fibers connect with interneurons having axodendritic, dendroaxonic, axoaxonic synapses on lamina I and II neurons, permitting both presynaptic and postsynaptic[25] modulation of the afferent volley.

The processing of all afferent information in the dorsal horn is subject to ongoing modulation by a variety of local terminal systems, the cell bodies of which are found in the spinal cord (intrinsic) or in the brain stem (bulbospinal systems). Electrophysiologic studies have shown that such systems can powerfully modulate the encoding of high-threshold information.

Several receptor systems have been shown to modulate the spinal processing of nociceptive input, e.g., opioids (μ, δ, K), α_2-adrenergic, serotonergic, γ-aminobutyric acid (GABA), and adenosinergic receptors.[103]

Current evidence suggests that the receptor classes outlined previously are essentially independent, although they may exist on the same cell membrane and act through the same family of K^+ channels.

For the μ, δ, α_2, $GABA_b$, 5-HT, muscarinic, and A_1 adenosinergic receptors, agonist occupation results in a prominent increase in K^+ conductance, which is mediated by a G i/o protein.[88]

In addition to these segmental controls, LeBars et al[73] have shown that WDR neurons recorded in the lumbar dorsal horn are inhibited by frankly noxious stimuli applied to other noncontiguous areas of the body. These diffuse noxious inhibitory controls have been demonstrated on all spinothalamic and trigeminothalamic neurons[44] and are activated by visceral[97] as well as cutaneous afferences. Diffuse noxious inhibitory controls are supraspinal reflexes mediated by nuclei in the brain stem.[42]

Central Sensitization

Brief afferent-conditioning stimuli have recently been shown to induce prolonged changes in the receptive fields' properties of dorsal horn neurons.[11] These changes include both expansions in the size of receptive fields and a change in the types of stimuli that activate these cells. In fact, the receptive fields of many dorsal horn neurons also contain a subliminal zone of functional activity. When peripheral injury activates high-threshold afferents, they recruit the subliminal components of the receptive fields to a level where they become suprathreshold.[62] This phenomenon is due to long-lasting changes in the spinal cord and is called central sensitization (Fig. 3). What are the mechanisms behind this central sensitization? Peripheral injury stimulates Aδ-C fiber afferents, producing a fast transmitter-mediated excitatory input to dorsal horn neurons. L-Glutamate is likely to be involved in this fast excitatory postsynaptic potential by acting on N-methyl-D-aspartate (NMDA) or more probably on the Kainate/quisqualate (non-NMDA) receptors. The excitatory postsynaptic potentials will induce a short duration inward current. Simultaneous release of peptides like substance P or calcitonin gene-related peptide (co-released from the same terminal as the fast transmitters) produce a slow excitatory potential that induces further inward currents. The slow excitatory potential will remove the voltage-sensitive Mg^{2+} block of the NMDA-activated channel and provide the opportunity for temporal summation (Fig. 4).

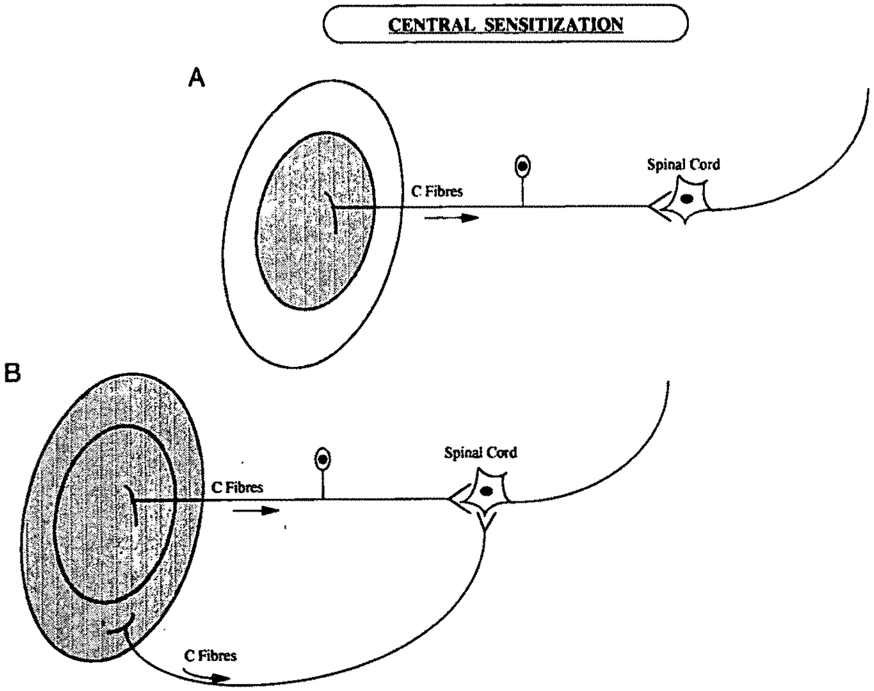


Figure 3. Central sensitization. *A,* The receptive fields of the dorsal horn neurons contain a subliminal zone of functional activity *(white area)* surrounding the "basal" receptive field *(gray area)*. *B,* After peripheral injury, the high-threshold afferents (C fibers) recruit the subliminal components of the receptive fields to a level where they become suprathreshold.

Importantly, NMDA receptors are not only involved in the induction but also in the maintenance of the central sensitization.[116] A characteristic of WDR neurons is the phenomenon of "wind up," a progressive increase in response to repeated C-fiber stimulation. This correlates with reports of increasing pain sensation with repetitive stimulation in humans.[92] Furthermore, these cells continue firing after the termination of C-nociceptor activity (postdischarge), in agreement with reports that the sensation of burning pain persists longer than the discharge of C nociceptors.[72]

On the other hand, the changes in second messengers may modify excitability for prolonged periods by phosphorylating ion channels or altering gene expression.[61]

Clinical Applications

The clinical significance of central sensitization lies in the following therapeutic predictions:

If the signal of peripheral injury were prevented from gaining access to the CNS, pain would be diminished. In order to prevent the

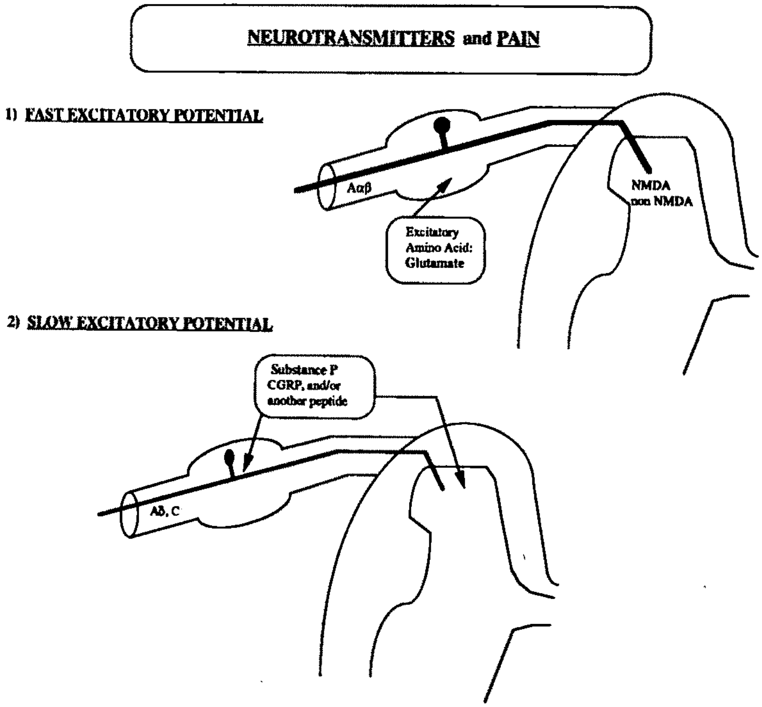

NEUROTRANSMITTERS and PAIN
1) FAST EXCITATORY POTENTIAL
Aαβ
Excitatory Amino Acid: Glutamate
NMDA
non NMDA
2) SLOW EXCITATORY POTENTIAL
Substance P CGRP, and/or another peptide
Aδ, C

Figure 4. Mechanisms of central sensitization. C fiber afferents produce a fast transmitter (L-glutamate) excitatory input to (non) NMDA receptors of dorsal horn neurons, inducing a short-duration inward current. From the same terminal, simultaneous release of peptides, such as substance P (and/or one of the 20 peptides found in primary sensory neurons), produce a slow excitatory potential that induces further inward currents. The slow excitatory potential removes the Mg^{++} block of the NMDA-activated channel, providing the opportunity for temporal summation (wind-up). Large-diameter fibers (Aαβ) are involved in the maintenance of central sensitization through excitatory input on (non) NMDA receptors. For further explanation, see text.

afferent barrage to produce the central sensitization, two approaches can be used. The use of local anesthetics before surgical intervention has been found to reduce postoperative pain when compared with the use of a general anesthetic without local block at the site of injury.[108] Opiate premedication increased the time to first request for postoperative analgesia in patients having orthopedic surgery.[80]

If an abnormal hyperexcitable state is already present (hyperalgesia, allodynia) the use of NMDA antagonists will be useful. Moreover, compared with opioids, NMDA antagonists (ketamine) show a potential role in preemptive analgesia.[81]

Afferent Pathways

The anterolateral ascending tracts have long been known to contain the major pathway for transmission of nociceptive information from the dorsal horn to the brain. Anterolateral cordotomy was the standard neurosurgical procedure for intractable pain, and the success of this operation was considered to be due to the section of the spinothalamic tract, the most clearly associated with pain sensation. Although this tract is a major pathway to the brain, it has become evident that the anterolateral quadrant contains a variety of other tracts involved in nociception, and that there are tracts transmitting nociceptive information in other quadrants, explaining the dissipation and occasional failure of cordotomy.

Spinothalamic tract neurons are located for the most part in laminae IV to VI of the dorsal horn, but also in the intermediate zone (lamina VII) and the ventral horn (lamina VIII).[113] The axons cross the midline at the level of the anterior commissure of the same segment as the cell bodies. They terminate mainly in four nuclei of the thalamus: the ventroposterolateral, posterior, central lateral, and submedius areas.[3] These areas are also in part the termination site of dorsal column nuclei and can be expected to send information to the sensory-motor cortex, much like the dorsal column pathway.

The reticular formation, which controls the level of arousal, has been shown to play an important part in nociception.[14, 53] Although not involved in the sensory-discriminative aspect of pain sensation, the reticular formation and its nuclei are thought to contribute to the triggering of pseudoaffective reflexes associated with nociception.[113] The characteristics of the spinoreticular tract are less well established than those of the spinothalamic tract, and there are no studies on the origin of the tract in humans. In monkeys, the spinoretricular tract neurons are located mostly in laminae VII and VIII.[4, 31, 47, 48] Retrograde tracing by unilateral injection of horseradish peroxydase in the medullary reticular formation labels cells bilaterally at the super cervical level.[67] In the lower cervical and lumbospinal cord, cells are more frequently labeled contralaterally. The spinoreticular tract projects largely onto the bulbopontine reticular formation nuclei, notably the nucleus gigantocellularis and nucleus raphe magnus. Stimulation of the nucleus raphe magnus in animals results in profound depression of dorsal horn neurons,[89] indicating a role in the descending tonic inhibitory system. The spinoreticular tract also shows dense projections onto the lateral reticular nucleus, a relay to the cerebellum, whose role in nociception has not yet been established.

The spinomesencephalic tract is a direct connection to the midbrain reticular formation, yet is organized differently than the spinoretricular tract of which it is sometimes considered an extension. The spinomesencephalic tract neurons are dispersed throughout the spinal gray matter, both dorsal and ventral horns. A large contingent of fibers originating in the dorsal horn are from lamina I neurons.[83, 84, 90, 104] Their axons often cross the midline, but a nonnegligible direct component is present in the midbrain. This tract projects onto the periaqueductal gray matter, an area important in the control of nociception. Stimulation of the periaqueductal gray matter results in analgesia and has been tried as a treatment for chronic pain in humans. This stimulation-induced analgesia is partly reversible by naloxone, indicating a role in a descending opioidergic pathway. However, the periaqueductal gray matter has no direct projections to the spinal cord. The antinociceptive effect is achieved by activation of the nucleus raphe magnus.

Painful stimuli have also been shown to activate hypothalamic neurons.[65] Retrograde tracing techniques in the monkey have identified a direct nociceptive connection to the hypothalamus and forebrain, regions believed to be involved in the elaboration of emotional behaviors. These spinohypothalamic and spinotelencephalic tracts[24] have the same origin as the spinothalamic tract, with the addition of neurons from an area adjacent to the central canal. A large contingent (40%) of spinohypothalamic tract fibers go on to terminate on the ipsilateral forebrain.

The spinocervical tract is a pathway in the dorsal part of the spinal cord that may play a role in nociception. Once again, there are no studies on the origin of this tract in humans; however, in monkeys, it originates mainly from lamina IV dorsal horn neurons.[18-20, 29, 40] The axons descend in the ipsilateral dorsolateral quadrant and terminate in the lateral cervical nucleus. From this, nucleus fibers then cross the midline to terminate on the ventrobasal complex of the thalamus, where they overlap the terminations of the spinothalamic tract and dorsal column nuclei.[8, 9]

Although the dorsal columns are primarily responsible for the transmission of tactile and proprioceptive information from primary afferent Aβ fibers, there exist postsynaptic fibers originating from the medial part of the ipsilateral dorsal horn.[11] These secondary neurons, localized for the most part in laminae III and IV, have dendrites extending dorsally up to the substantia gelatinosa,[16] suggesting their activation by unmyelinated afferents. Electrophysiologic studies have shown that these neurons are activated by nociceptive stimuli, and that there exist nociceptive nonspecific neurons in the nuclei of Goll and Burdach that project to the thalamus. However, a section of the dorsal columns does not seem to affect nociceptive thresholds, and the role of these neurons is not yet clear. On the other hand, dorsal column stimulation by epidural electrodes does have therapeutic effects, and the resulting analgesia may be produced by the inhibitory action of the collaterals given off by large-diameter fibers along the length of the dorsal column or by retrograde activation of dorsal horn neurons.

SUMMARY

In this article, we have reviewed the different stages of acquisition and processing of nociceptive information from peripheral receptor to brain and underline the plastic changes that accompany tissue injury.

For instance, the subclassification of peripheral receptors in nociceptors and non-nociceptors (e.g., mechanoreceptors, thermoreceptors).

must be understood in light of peripheral sensitization. This phenomenon is the probable explanation for primary hyperalgesia, the decrease in pain threshold at the site of injury.

The observation that substance P enhances NMDA-elicited responses suggests that these two receptor systems may operate in concert to prolong and amplify the afferent input generated by peripheral tissue injury. Such afferent barrage induces a state of central sensitization.

In this phenomenon, the subliminal zone of the receptive fields of many dorsal horn neurons becomes suprathreshold. These peripheral and central sensitizations probably induce permanent changes in central circuits associated with some chronic pain states.

In fact, it is tempting to extrapolate from Bach et al[5] that preventive treatment of acute pain will prevent the development of chronic pain syndromes in surgical patients.

References

1. Adriaensen H, Gybels J, Handwerker HO, et al: Nociceptor discharges and sensations due to prolonged noxious mechanical stimulation—A paradox. Hum Neurobiol 3:53, 1984
2. Albe-Fessard D: Central nervous mechanisms involved in pain and analgesia. *In* Lim RKS (ed): Pharmacology of Pain. Oxford, Pergamon, 1968, p 131
3. Albe-Fessard D, Berkeley K, Kruger L, et al: Diencephalic mechanisms of pain sensation. Brain Res Rev 9:217, 1985
4. Albe-Fessard D, Levante A, Lamour Y: Origin of spinothalamic and spinoreticular pathways in cats and monkeys. *In* Bonica JJ (ed): Advances in Neurology, ed 4. New York, Raven, 1974, p 157
5. Bach S, Noreng MF, Tjellden NV: Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural brockade. Pain 33:297, 1988
6. Bartho L, Szolcsanyi J: Opiate agonists inhibit neurogenic plasma extravasation in the rat. Eur J Pharmacol 73:101, 1981
7. Beck PH, Handwerker HO, Zimmermann M: Nervous outflow from the cat's foot-pad during noxious radiant heat stimulation. Brain Res 67:373, 1974
8. Berkley KJ: Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cats and monkeys. I. Ascending somatic sensory inputs to the lateral diencephalon. J Comp Neurol 193:283, 1980
9. Berkley KJ: Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cats and monkeys. II. Cerebellar projections compared with those of the ascending somatic sensory pathways in the lateral diencephalon. J Comp Neurol 220:229, 1983
10. Besson JM, Catchlove RFH, Felz P, et al: Further evidence for post-synaptic inhibitions on lamina V dorsal horn interneurons. Brain Res 66:531, 1974
11. Besson JM, Chaouach A: Peripheral and spinal mechanisms of nociception. Physiol Rev 67:67, 1987
12. Bessou P, Perl ER: Response of cutaneous sensory units with unmyeliated nerve fibers to noxious stimuli. J Neurophysiol 32:1025, 1969
13. Blix M: Experimenteller Beitrag zur Lösung der Frage über die Specifiche Energie der Hautnerven. Z Biol 20:141, 1884
14. Bowsher D: Role of the reticular formation in responses to noxious stimulation. Pain 2:361, 1976
15. Bromm B, Jahnke MT, Treede RD: Responses of human cutaneous afferents to CO_2 laser stimuli pain. Exp Brain Res 55:158, 1984

16. Brown AG: The termination of cutaneous nerve fibers in the spinal cord. Trends Neuro Sci 4:64, 1981
17. Brown AG, Fyffe REW: Form and function of dorsal horn neurons with axons ascending the dorsal columns in cat. J Physiol (Lond) 321:31, 1981
18. Brown AG, Rose PK, Snow PJ: The morphology of spinocervical tract neurons revealed by intracellular injection of horseradish peroxidase. J Physiol (Lond) 270:747, 1977
19. Bryan N, Trevino DL, Coulter JD, et al: Location and somatotopic organisation of cells of origin of the spinocervical tract. Exp Brain Res 17:177, 1973
20. Bryan RN, Coulter JD, Willis WD: Cells of origin of the spinocervical tract in the monkey. Exp Neurol 42:578, 1974
21. Buck SH, Walsh JH, Yamamura HT: Neuropeptides in sensory neurons. Life Sci 30:1857, 1982
22. Burgess PR, Clark FJ: Characteristics of knee joint receptors in the cat. J Physiol (Lond) 203:317, 1969
23. Burgess PR, Perl ER: Myelinated afferent fibers responding specifically to noxious stimulation of the skin. J Physiol (Lond) 190:541, 1967
24. Burstein R, Cliffer KD, Giesler GJ Jr: Direct somatosensory projection from the spinal cord to the hypothalamus and telencephalon. J Neurosci 7:4159, 1987
25. Campbell JN, Meyer RA, Lamotte RH: Sensitization of myelinated nociceptive afferents that innervate the monkey hand. J Neurophysiol 42:1669, 1979
26. Campbell JN, Raja SN, Cohen RH, et al: Peripheral neural mechanisms of nociception. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 22
27. Celander O, Folkow B: The nature and the distribution of afferent fibers provided with the axon reflex arrangement. Acta Physiol Scand 29:359, 1953
28. Cervero F: Neurophysiology of gastrointestinal pain. Baillieres Clin Gastroenterol 2:183, 1988
29. Cervero F, Iggo A, Molony V: Responses of spinocervical tract neurons to noxious stimulation of the skin. J Physiol (Lond) 267:537, 1977
30. Cervero F: Visceral Pain. *In* Dubner R, Gebhart GF, Bond MR (eds): Proceedings of the Vth World Congress on Pain. Amsterdam, Elsevier, 1988, p 216
31. Cervero F, Wolstencroft JH: A positive feedback loop between spinal cord nociceptive pathways and antinociceptive areas of the cat's brain stem. Pain 20:125, 1984
32. Clifton GL, Coggeshall RE, Vance WH: Receptive fields of unmyelinated ventral root afferents in the cat. J Physiol (Lond) 256:573, 1976
33. Coderre TJ, Abbott FV, Melzak R: Effects of peripheral antisympathetic treatments in the tail-flick, formalin, and autotomytests. Pain 18:13, 1984
34. Coggeshall RE, Applebaum ML, Fazen M, et al: Unmyelinated afferents in human ventral roots, a possible explanation for the failure of dorsal rhizotomy to relieve pain. Brain 98:157, 1975
35. Coggeshall RE, Coulter JD, Willis WD: Unmyelinated axons in the ventral root of the cat lumbosacral enlargement. J Comp Neurol 272:39, 1983
36. Coggeshall RE, Hong KAP, Langford LA, et al: Discharge characteristics of fine medial articular afferents at rest and during passive movements of inflamed knee joints. Brain Res 272:185, 1983
37. Coggeshall RE, Ito H: Sensory fibers in ventral roots L5 and S1 in the cat. J Physiol (Lond) 267:215, 1977
38. Cohen RH, Meyer RA, Davis KD, et al: Mechanically insensitive afferents (MIAs) in cutaneous nerves of monkey. Pain Suppl 5:S105, 1990
39. Collins WF, Nulsen FE, Randt CT: Relation of peripheral nerve fiber size and sensation in man. Arch Neurol Psychiatr 3:381, 1960
40. Craig AD Jr: Spinal and medullary input to the lateral cervical nucleus. J Comp Neurol 181:729, 1978
41. Craig KD: Emotional aspects of pain. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 220
42. De Broucker T, Cesaro P, Willer JC, et al: Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain 113:1223, 1990
43. DeGroat WC: Spinal cord projections and neuropeptides in visceral afferent neurons.

In Cervero F, Morrison JFB (eds): Visceral Sensation: Progress in Brain Research. Amsterdam, Elsevier, 1986, p 165

44. Dickenson AH, LeBars D: Diffuse noxious inhibitory controls (DNIC) involve trigemino- and spinothalamic neurones in the rat. Exp Brain Res 49:174, 1983
45. Dray A, Perkins MN: Bradykinin activates peripheral capsaicin-sensitive fibres via a second messenger system. Agents Actions 25:214, 1988
46. Ferriera SM: Prostaglandins, aspirin-like drugs, and analgesia. Nature 240:200, 1972
47. Fields HL, Clanton CH, Anderson SD: Somatosensory properties of spinoreticular neurones in the cat. Brain Res 120:49, 1977
48. Fields HL, Wagner GM, Anderson SD: Some properties of spinal neurones projecting to the medial brain stem reticularformation. Exp Neurol 47:118, 1975
49. Fitzgerald M: Capsaicin and sensory neurons—A review. Pain 15:109, 1983
50. Fitzgerald M: The course and termination of primary afferent fibers. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 47
51. Fitzgerald M, Lynn B: The sensitization of high threshold mechanoreceptors with myelinated axons by repeated heating. J Physiol (Lond) 265:549, 1977
52. Foreman JC, Jordan CC, Piotrowski W: Interaction of neurotensin with the substance P receptor mediating histamine release from rat mast cells and the flare in human skin. Br J Pharmacol 77:531, 1982
53. Guilbaud G, Peschanski M, Besson JM: Experimental data related to nociception and pain at the supraspinal level. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 141
54. Habler HJ, Janig W, Koltzenburg M: A novel type of unmyelinated chemosensitive nociceptor in the acutely inflamed urinary bladder. Agents Actions 25:219, 1988
55. Haley JE, Dickenson AH, Schachter M: Electrophysiological evidence for a role of bradykinin in chemical nociception in the rat. Neurosci Lett 97:198, 1989
56. Hillman P, Wall PD: Inhibitory and excitatory factors influencing the receptive fields of lamina V spinal cord cells. Exp Brain Res 9:284, 1969
57. Hinsey JC, Gasser HS: The component of the dorsal root mediating vasodilatation and the Sherrington contracture. Am J Physiol 92:679, 1930
58. Hoffman DS, Dubner R, Hayes RL, et al: Neuronal activity in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. I. Response to innocuous and noxious thermal stimuli. J Neurophysiol 46:409, 1981
59. Hongo T, Jankowska E, Lundberg A: Post-synaptic excitation and inhibition from primary afferent neurons in the spinocervical tract. J Physiol (Lond) 199:569, 1968
60. Hunt CC, McIntyre AK: An analysis of fiber diameter and receptor characteristics of myelinated cutaneous afferent fibers in cat. J Physiol (Lond) 153:99, 1960
61. Hunt SP, Pini A, Evan G: Induction of C-fos-like protein in spinal cord neurones following sensory stimulation. Nature 328:632, 1987
62. Hylden JLK, Nahin RL, Traub RJ, et al: Expansion of receptive fields of spinal of spinal lamina I projection neurones in rats with unilateral adjuvant-induced inflammation: The contribution of dorsal horn mechanisms. Pain 37:229, 1989
63. Iruichijima J, Zotterman Y: The specificity of afferent cutaneous C fibers in mammals. Acta Physiol Scand 49:267, 1960
64. Jessel TM, Dodd J: Functional chemistry of primary afferent neurons. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 82
65. Kanosue K, Nakayama T, Ishikawa Y, et al: Responses of hypothalamic and thalamic neurons to noxious and scrotal thermal stimulations in rats. J Therm Biol 9:11, 1984
66. Kenshalo DR Jr, Leonard RB, Chung JM, et al: Responses of primate spinothalamic neurons to graded and repeated noxious heat stimuli. J Neurophysiol 42:1370, 1979
67. Kevetter GA, Haber LH, Yezierski RP, et al: Cells of origin of the spinoreticular tract in the monkey. J Comp Neurol 207:61, 1982
68. Khalil Z, Helme RD: Sympathetic neurons modulate plasma extravasation in the rat through a non-adrenergic mechanism. Clin Exp Neurol 26:45, 1989
69. Kumazawa T, Mizumura K: The polymodal C-fiber receptor in the muscle of the dog. Brain Res 101:589, 1976
70. Kumazawa T, Mizumura K: Thin-fiber receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. J Physiol (Lond) 273:179, 1977

71. Lamotte RH, Simone DA, Baumann TK, et al: Hypothesis for novel classes of chemoreceptors mediating chemogenic pain and itch. *In* Dubner R, Gebhart GF, Bond MR (eds): Proceedings of the Vth World Congress on Pain, Amsterdam, Elsevier, 1988, p 529
72. Lamotte RH, Thalhammer JG, Torebjork E, et al: Peripheral neural mechanisms of cutaneous hyperalgesia following mild injury by heat. J Neurosci 2:765, 1982
73. LeBars D, Dickenson AH, Besson JM: Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurons in the rat. Pain 6:283, 1979
74. LeBars D, Dickenson AH, Besson JM, et al: Aspects of sensory processing through convergent neurons. *In* Yaksh TL (eds): Spinal Afferent Processing. New York, Plenum, 1986, p 467
75. Leeman SE, Gamse R: Substance P in sensory neurons. Trends Pharmacol Sci 2:119, 1981
76. Lembeck F, Donnerer J: Opioid control of the function of primary afferent substance P fibers. Eur J Pharmacol 114:241, 1985
77. Levine JD, Lau W, Kwiat G, et al: Leukotriene B4 produces hyperalgesia that is dependant on polymorphonuclear leukocytes. Science 225:225, 1984
78. Lewis T: Pain. New York, MacMillan, 1942
79. Lynn B, Shakhanbeh J: Neurogenic inflammation in the skin of the rabbit. Agents Actions 25:228, 1988
80. McQuay HS, Caroll D, Moore RA: Post operative orthopedic pain. The effect of opiate premedication and local anesthetic blocks. Pain 33:291, 1988
81. Maurset A, Skoglund LA, Husveit O, et al: Comparison of ketamine and pethidine in experimental and postoperative pain. Pain 36:37, 1989
82. Melzak R, Wall PD: Pain mechanisms: A new theory. Science 150:971, 1965
83. Menetrey D, Chaouach A, Besson JM: Location and properties of dorsal horn neurons at origin of spinoreticular tract in the lumbar enlargement of the rat. J Neurophysiol 44:862, 1980
84. Menetrey D, Chaouach A, Binder D, et al: The origin of the spinomesencephalic tract in the rat: An anatomical study using the retrograde transport of horseradish peroxidase. J Comp Neurol 206:193, 1982
85. Meyer RA, Campbell JN: A novel electrophysiological technique for locating cutaneous nociceptive and chemospecific receptors. Brain Res 441:81, 1988
86. Nafe JP: A quantitative theory of feeling. J Gen Psychol 2:199, 1929
87. Neugebauer V, Schaible HG: Peripheral and spinal components of the sensitization of spinal neurons during an acute experimental arthritis. Agents Actions 25:234, 1988
88. North RA, Williams JT, Surprenant A, et al: μ and δ receptors belong to a family of receptors that are coupled to potassium channels. Proc Nat Acad Sci USA 84:5487, 1987
89. Oliveras JL, Redjemi F, Guilbaud G, et al: Analgesia induced by electrical stimulation of the inferior central nucleus of the raphe in the cat. Pain 1:139, 1975
90. Panneton WP, Burton H: Projections from the paratrigeminal nucleus and the medullary and spinal dorsal horns in the peribrachial area of the cat. Neuroscience 15:779, 1985
91. Pernow B: Substance P—a putative mediator of antidromic vasodilatation. Gen Pharmacol 14:13, 1983
92. Price DD: Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol 37:371, 1972
93. Price DD, Hayashi H, Dubner R, et al: Functional relationships between neurons of marginal and substantia gelatinosa layers of the primate dorsal horn. J Neurophysiol 42:1590, 1979
94. Price DD, Mayer DJ: Physiological laminar organisation of the dorsal horn of M. mulatta. Brain Res 79:321, 1974
95. Price DD, Wagman IH: The physiological role of A and C fiber inputs to the dorsal horn of M. mulatta. Exp Neurol 29:373, 1970
96. Raja SN, Meyer RA, Campbell JN: Peripheral mechanisms of somatic pain. Anesthesiology 68:571, 1988
97. Ren K, Randich A, Gebhart GF: Effects of electrical stimulation of vagal afferents on spinothalamic tract cells in the rat. Pain 44:311, 1991

98. Rexed B: A cytoarchitectonic atlas of the spinal cord in the cat. J Comp Neurol 100:297, 1954
99. Schaible HG, Schmidt RF: Direct observation of the sensitization of articular afferents during an experimental arthritis. *In* Dubner R, Gebhart GF, Bond MR (eds): Proceeding of the Vth World Congress on Pain, Amsterdam, Elsevier, 1988, p 44
99a. Sherrington CS: The Integrative Action of the Nervous System. New Haven, CT, Yale University Press, 1906
100. Shyu B, Huang KH, Rydenhag B, et al: Sympathetic effects on C-fiber responses. Pain Suppl 2:S9, 1982
101. Sinclair DC: Cutaneous sensation and the doctrine of specific energy. Brain 78:584, 1955
102. Smith TW, Buchan P: Peripheral opioid receptors located in the rat saphenous nerve. Neuropeptides 5:217, 1984
103. Sosnowski M, Yaksh TL: Spinal administration of receptor-selective drugs as analgesics: New horizons. J Pain Symptom Management 5:204, 1990
104. Swett JE McMahon SB, Wall PD: Long ascending projections to the midbrain from cells of lamina I and nucleus of the dorsolateral funiculus of the rat spinal cord. J Comp Neurol 238:401, 1985
105. Szolcsanyi J: Antidromic vasodilatation and neurogenic inflammation. Agents Actions 23:4, 1988
106. Theoharides TC, Douglas WW: Mast cell histamine secretion in response to somatostatin analogues: Structural considerations. Eur J Pharmacol 73:131, 1981
107. Torebjork E: Nociceptor activation and pain. Philos Trans R Soc Lond [Biol] 308:227, 1985
108. Tverkoy M, Cozacov C, Ayache M, et al: Postoperative pain after herniorraphy with different types of anesthesia. Anesth Analg 70:29, 1990
109. Wagman IH, Price DD: Responses of dorsal horn cells of M. mulatta to cutaneous and sural nerve A and C-fiber stimulation. J Neurophysiol 32:803, 1969
110. Wall PD: The laminar organisation of the dorsal horn and effects of descending impulses. J Physiol (Lond) 188:403, 1967
111. Wall PD: The gate control theory of pain mechanisms. A re-examination and re-statement. Brain 101:18, 1978
112. White DM, Basbaum AI, Goetzl EJ, et al: The 15-lipoxygenase product, 8R, 15S-diHETE, stereospecifically sensitizes C-fiber mechanoheat nociceptors in hairy skin of rat. J Neurophysiol 63:966, 1990
113. Willis WD: The origin and destination of pathways involved in pain transmission. *In* Wall PD, Melzak R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 112
114. Willis WD, Trevino DL, Coulter JD, et al: Responses of primate spinothalamic tract neurons to natural stimulation of the hindlimb. J Neurophysiol 37:358, 1974
115. Witt I, Griffin JP: Afferent cutaneous C-fiber reactivity to repeated thermal stimuli. Nature 194:776, 1962
116. Woolf CJ, Thompson SWN: The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic receptor activation; implications for the treatment of post-injuring pain hypersensitivity states. Pain 44:293, 1991

Address reprint requests to

M. Sosnowski, MD, PhD
Department of Anesthesiology
Institut J. Bordet
Université Libre de Bruxelles
1 Rue Héger Bordet
Brussels 1000, Belgium

CURRENT CONCEPTS OF ACUTE PAIN CONTROL 0889-8537/92 $0.00 + .20

MEASUREMENT OF PAIN

Joel Katz, PhD, and Ronald Melzack, PhD

Pain is a personal, subjective experience influenced by cultural learning, the meaning of the situation, attention, and other psychological variables.[66] Pain processes do not begin with the stimulation of receptors. Rather, injury or disease produces neural signals that enter an active nervous system that (in the adult organism) is the substrate of past experience, culture, anxiety, and depression. These brain processes actively participate in the selection, abstraction, and synthesis of information from the total sensory input. Pain, then, is not simply the end product of a linear sensory transmission system; rather, it is a dynamic process that involves continuous interactions among complex ascending and descending systems.

DIMENSIONS OF PAIN EXPERIENCE

Research on pain, since the beginning of this century, has been dominated by the concept that pain is purely a sensory experience. Yet pain also has a distinctly unpleasant, affective quality. It becomes overwhelming, demands immediate attention, and disrupts ongoing behavior and thought. It motivates or drives the organism into activity aimed at stopping the pain as quickly as possible. To consider only the sensory features of pain and ignore its motivational-affective properties is to look at only part of the problem. Even the concept of pain as a perception, with full recognition of past experience, attention, and other cognitive influences, still neglects the crucial motivational dimension.

Department of Psychology, Toronto General Division, The Toronto Hospital; Departments of Behavioral Science and Anesthesia, University of Toronto, Toronto, Ontario; and Department of Psychology, McGill University, Montreal, Quebec, Canada

These considerations led Melzack and Casey[61] to suggest that there are three major psychological dimensions of pain: sensory-discriminative, motivational-affective, and cognitive-evaluative. They proposed that these dimensions of pain experience are subserved by physiologically specialized systems in the brain. Melzack and Casey[61] proposed that the sensory-discriminative dimension of pain is influenced primarily by the rapidly conducting spinal systems. The powerful motivational drive and unpleasant effects, characteristic of pain, are subserved by activities in reticular and limbic structures that are influenced primarily by the slowly conducting spinal systems. Neocortical or higher central nervous system (CNS) processes, such as evaluation of the input in terms of past experience, exert control over activity in both the discriminative and motivational systems.

It is assumed that these three categories of activity interact with one another to provide perceptual information on the location, magnitude, and spatiotemporal properties of the noxious stimuli, motivational tendency toward escape or attack, cognitive information based on past experience, and probability of outcome of different response strategies.[61] All three forms of activity could then influence motor mechanisms responsible for the complex pattern of overt responses that characterize pain.

THE LANGUAGE OF PAIN

Clinical investigators have long recognized the varieties of pain experience. Descriptions of the burning qualities of pain after peripheral nerve injury, or the stabbing, cramping qualities of visceral pains frequently provide the key to diagnosis and may even suggest the course of therapy. Despite the frequency of such descriptions and the seemingly high agreement that such adjectives are valid descriptive words, studies of their use and meaning are relatively recent.

Anyone who has suffered severe pain and tried to describe the experience to a friend or to the doctor often finds himself or herself at a loss for words. The reason for this difficulty in expressing pain experience is not because the words do not exist. As we shall soon see, there is an abundance of appropriate words. Rather, the main reason is that, fortunately, they are not words that we have occasion to use often. Another reason is that the words may seem absurd. We may use descriptors such as splitting, shooting, gnawing, wrenching, or stinging, but there are no external objective references for these words. If we talk about a blue pen or a yellow pencil we can point to an object and say "that is what I mean by yellow" or "this color of the pen is blue." But what can we point to to tell another person precisely what we mean by smarting, tingling, or rasping? A person who suffers terrible pain may say that the pain is burning and add that "it feels as if someone is shoving a red-hot poker through my toes and slowly twisting it around." These "as if" statements are often essential to convey the qualities of the experience.

If the study of pain in people is to have a scientific foundation, it is essential to measure it. If we want to know how effective a new drug is, we need numbers to say that the pain decreased by some amount. Yet, while this is important to know, we also want to know whether the drug specifically decreased the burning quality of the pain, or if the especially miserable, tight, cramping feeling is gone.

APPROACHES TO THE MEASUREMENT OF PAIN

Until recently, the methods that were used for pain measurement treated pain as though it were a single unique quality that varies only in intensity.[2] These methods include the use of verbal rating scales (e.g., mild, moderate, severe), numerical rating scales (1–100), and visual analogue scales (VAS).[36, 39] These simple methods have all been used effectively in hospital clinics and have provided valuable information about pain and analgesia. The visual analogue pain scale[36] and the McGill Pain Questionnaire[57] have been used extensively in clinical settings. The Descriptor Differential Scale[25] has been used mainly in studies of experimental pain, but has recently been extended to pain measurement in a clinical setting.[22] These three instruments offer several advantages over other self-rating scales.

Visual Analogue Scales

The VAS provides a simple, efficient, and minimally intrusive measure of pain intensity that has been used widely in clinical and research settings where a quick index of pain is required and to which a numerical value can be assigned. The VAS consists of a 10-cm horizontal[37] or vertical[75, 76] line with the two endpoints labeled "no pain" and "worst pain ever" (or a similar verbal descriptor representing the upper pole). The patient is required to mark the 10-cm line at a point that corresponds to the level of pain intensity he or she presently feels. The distance in centimeters from the low end of the VAS and the patient's mark is used as a numerical index of the severity of pain.

The VAS is sensitive to pharmacologic and nonpharmacologic procedures that alter the experience of pain[1, 3, 8, 14, 86] and correlates highly with pain measured on verbal and numerical rating scales.[17, 49, 68] Instructions to patients to rate the amount or percentage of pain relief using a VAS (e.g., following administration of a treatment designed to reduce pain) may introduce unnecessary bias (e.g., expectancy for change and reliance on memory), which reduces the validity of the measure.[5] It has been suggested,[5] therefore, that a more appropriate measure of change may be obtained by having patients rate the absolute amount of pain at different points in time (e.g., before and after the intervention, but see Ekblom and Hansson[17]).

A major advantage of the VAS as a measure of sensory pain

P24625

intensity is its ratio scale properties.[69, 70] In contrast to many other pain measurement tools, equality of ratios is implied, making it appropriate to speak meaningfully about percentage differences between VAS measurements obtained either at multiple points in time or from independent samples of subjects. Thus, ratio statements may be made that describe pain in one group of patients as being several times that of another or as being reduced by a certain percentage. The ratio scale property of the VAS also means the measurements are suitable for description using parametric statistics (such as the mean, standard deviation, and Pearson product-moment correlation coefficient) and are amenable to parametric inferential statistical procedures (such as analysis of variance and regression analysis). Other advantages of the VAS include (1) its ease and brevity of administration and scoring,[38] (2) minimal intrusiveness, and, (3) providing that adequately clear instructions are given to the patient, its conceptual simplicity.[6, 37]

The major disadvantage of the VAS is its assumption that pain is a unidimensional experience.[22, 57] Although intensity is, without a doubt, a salient dimension of pain, it is clear that the word *pain* refers to an endless variety of qualities that are categorized under a single linguistic label, not to a specific, single sensation that varies only in intensity. Each pain has unique qualities. The pain of a toothache is obviously different from that of a pinprick, just as the pain of a coronary occlusion is uniquely different from the pain of a broken leg. To describe pain solely in terms of intensity is like specifying the visual world only in terms of light flux, without regard to pattern, color, texture, and the many other dimensions of visual experience.

The McGill Pain Questionnaire

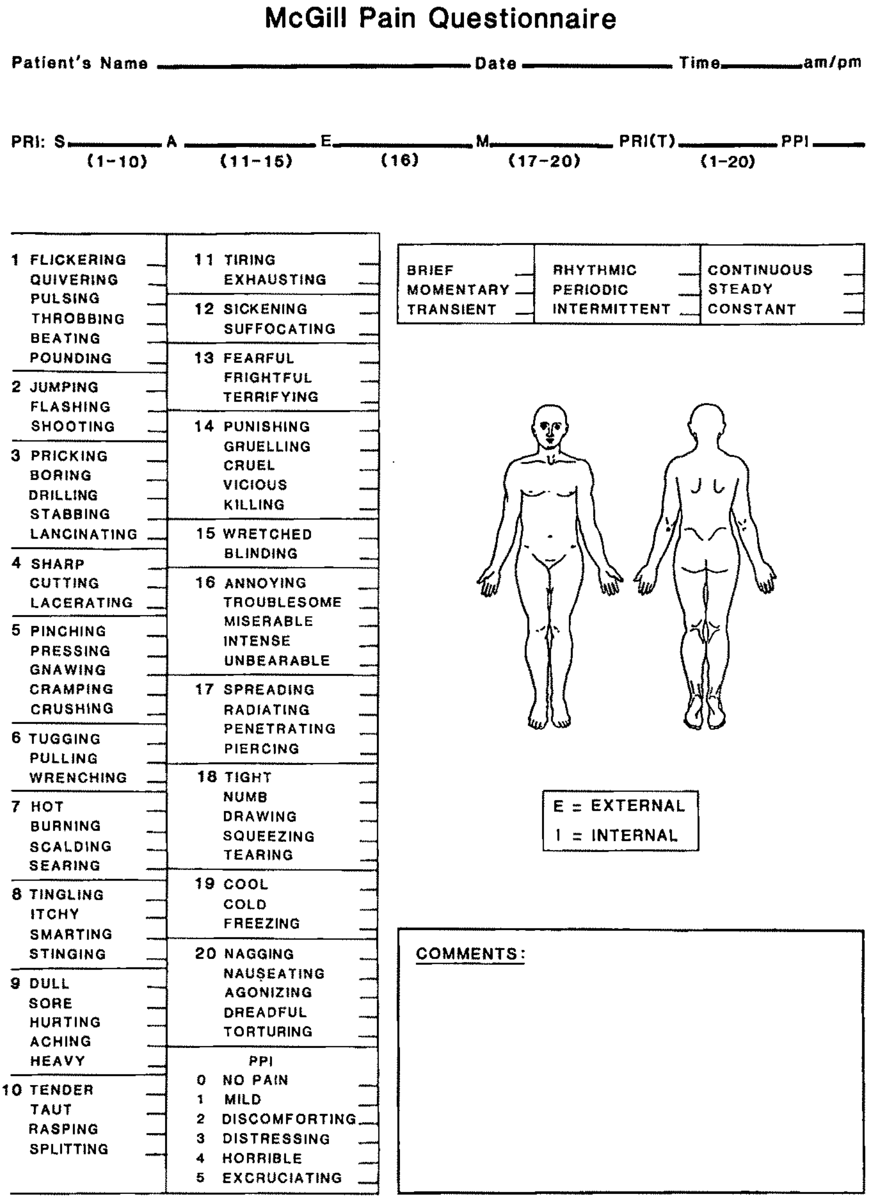
Development and Description

Melzack and Torgerson[65] have made a start toward specifying the qualities of pain. In the first part of their study, physicians and other university graduates were asked to classify 102 words, obtained from the clinical literature, into small groups that describe distinctly different aspects of the experience of pain. On the basis of the data, the words were categorized into three major classes and 16 subclasses (Fig. 1). The classes are (1) words that describe the *sensory qualities* of the experience in terms of temporal, spatial, pressure, thermal, and other properties; (2) words that describe *affective qualities* in terms of tension, fear, and autonomic properties that are part of the pain experience; and (3) *evaluative* words that describe the subjective overall intensity of the total pain experience. Each subclass, which was given a descriptive label, consists of a group of words that were considered by most subjects to be qualitatively similar. Some of these words are undoubtedly synonyms, others seem to be synonymous but vary in intensity, whereas many provide subtle differences or nuances (despite their similarities) that may be of importance to a patient who is trying desperately to communicate to a physician.

The second part of the study was an attempt to determine the pain intensities implied by the words within each subclass. Groups of physicians, patients, and students were asked to assign an intensity value to each word, using a numerical scale ranging from least (or mild) pain to worst (or excruciating) pain. When this was done, it was apparent that several words within each subclass had the same relative-intensity relationships in all three sets. For example, in the spatial subclass, "shooting" was found to represent more pain than "flashing," which in turn implied more pain than "jumping." Although the precise intensity scale values differed for the three groups, all three agreed on the positions of the words relative to each other. The scale values of the words for patients, based on the precise numerical values listed in Melzack and Torgerson,[65] are indicated in Figure 1.

Because of the high degree of agreement on the intensity relationships among pain descriptors by subjects who have different cultural, socioeconomic, and educational backgrounds, a pain questionnaire (Fig. 2) was developed as an experimental tool for studies of the effects of various methods of pain management. In addition to the list of pain descriptors, the questionnaire contains line drawings of the body to show the spatial distribution of the pain, words that describe temporal properties of pain, and descriptors of the overall present pain intensity. The present pain intensity is recorded as a number from 1 to 5, in which each number is associated with the following words: 1, mild; 2, discomforting; 3, distressing; 4, horrible; and 5, excruciating. The mean scale values of these words, which were chosen from the evaluative category, are approximately equally far apart[65] so that they represent equal scale intervals and thereby provide "anchors" for the specification of the overall pain intensity.

In a preliminary study, the pain questionnaire consisted of the 16 subclasses of descriptors shown in Figure 1, as well as the additional information deemed necessary for the evaluation of pain. It soon became clear, however, that many of the patients found certain key words to be absent. These words were then selected from the original word list used by Melzack and Torgerson,[65] categorized appropriately, and ranked according to their mean scale values. A further set of words—cool, cold, freezing—was used by patients on rare occasions but was indicated to be essential for an adequate description of some types of pain. Thus, four supplementary, or "miscellaneous," subclasses were added to the word lists of the questionnaire (Fig. 2). The final classification, then, appeared to represent the most parsimonious and meaningful set of subclasses without at the same time losing subclasses that represent important qualitative properties. A description of the properties and scoring methods of the questionnaire, which is referred to as the McGill Pain Questionnaire, has been published,[57] and it has become a widely used clinical and research tool.[58, 73, 87]



McGill Pain Questionnaire

Patient's Name ____ Date ____ Time ____ am/pm

PRI: S ____ (1-10) A ____ (11-15) E ____ (16) M ____ (17-20) PRI(T) ____ (1-20) PPI ____

1 FLICKERING ____
QUIVERING ____
PULSING ____
THROBBING ____
BEATING ____
POUNDING ____

2 JUMPING ____
FLASHING ____
SHOOTING ____

3 PRICKING ____
BORING ____
DRILLING ____
STABBING ____
LANCINATING ____

4 SHARP ____
CUTTING ____
LACERATING ____

5 PINCHING ____
PRESSING ____
GNAWING ____
CRAMPING ____
CRUSHING ____

6 TUGGING ____
PULLING ____
WRENCHING ____

7 HOT ____
BURNING ____
SCALDING ____
SEARING ____

8 TINGLING ____
ITCHY ____
SMARTING ____
STINGING ____

9 DULL ____
SORE ____
HURTING ____
ACHING ____
HEAVY ____

10 TENDER ____
TAUT ____
RASPING ____
SPLITTING ____

11 TIRING ____
EXHAUSTING ____

12 SICKENING ____
SUFFOCATING ____

13 FEARFUL ____
FRIGHTFUL ____
TERRIFYING ____

14 PUNISHING ____
GRUELLING ____
CRUEL ____
VICIOUS ____
KILLING ____

15 WRETCHED ____
BLINDING ____

16 ANNOYING ____
TROUBLESOME ____
MISERABLE ____
INTENSE ____
UNBEARABLE ____

17 SPREADING ____
RADIATING ____
PENETRATING ____
PIERCING ____

18 TIGHT ____
NUMB ____
DRAWING ____
SQUEEZING ____
TEARING ____

19 COOL ____
COLD ____
FREEZING ____

20 NAGGING ____
NAUSEATING ____
AGONIZING ____
DREADFUL ____
TORTURING ____

PPI
0 NO PAIN ____
1 MILD ____
2 DISCOMFORTING ____
3 DISTRESSING ____
4 HORRIBLE ____
5 EXCRUCIATING ____

BRIEF ____	RHYTHMIC ____	CONTINUOUS ____
MOMENTARY ____	PERIODIC ____	STEADY ____
TRANSIENT ____	INTERMITTENT ____	CONSTANT ____

E = EXTERNAL
I = INTERNAL

COMMENTS:

Figure 2. McGill Pain Questionnaire. The descriptors fall into four major groups: sensory, 1 to 10; affective, 11–15; evaluative, 16; and miscellaneous, 17–20. The rank value for each descriptor is based on its position in the word set. The sum of the rank values is the pain rating index (PRI). The present pain intensity is based on a scale of 0 to 5. (*From* Melzack R: Psychological aspects of pain: Implications for neural blockade. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, ed 2. Philadelphia, Lippincott, 1988, p 845; with permission.)

Measures of Pain Experience

The descriptor lists of the McGill Pain Questionnaire are read to a patient, with the explicit instruction that he or she choose only those words that describe his or her feelings and sensations at that moment. Three major indices are obtained:

1. The pain rating index based on the rank values of the words: In this scoring system, the word in each subclass implying the least pain is given a value of 1, the next word is given a value of 2, and so forth. The values of the words chosen by a patient are summed to obtain a score separately for the sensory (subclasses 1–10), affective (subclasses 11–15), evaluative (subclass 16), and miscellaneous (subclasses 17–20) words, in addition to providing a total score (subclasses 1–20). Figure 3 shows McGill Pain Questionnaire scores (total score from subclasses 1–20) obtained by patients with a variety of acute and chronic pains.
2. The number of words chosen.
3. The present pain intensity: the number-word combination chosen as the indicator of overall pain intensity at the time of administration of the questionnaire.

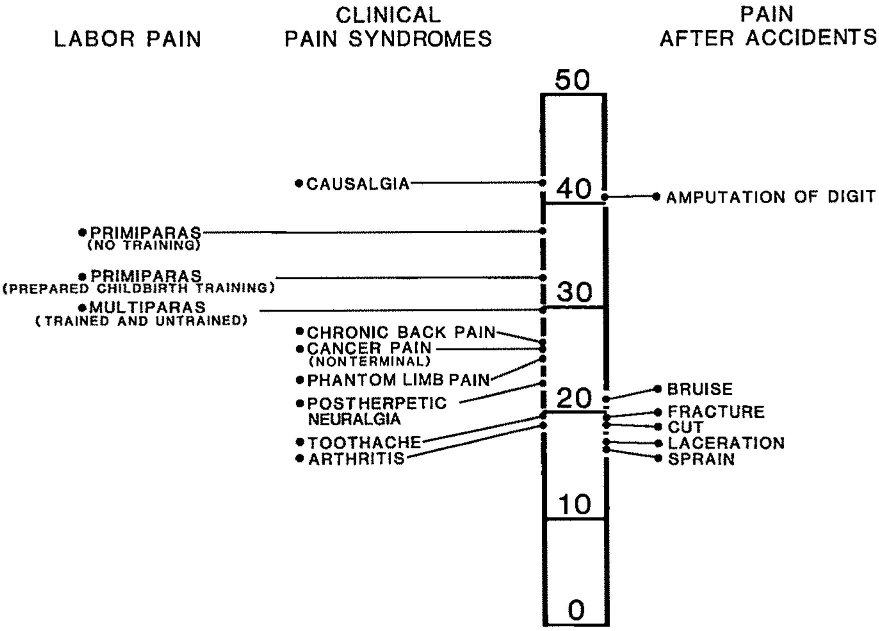


Figure 3. Comparison of pain scores using the McGill Pain Questionnaire obtained from women during labor[63] and from patients in a general hospital pain clinic[57] and an emergency department.[67] The pain score for causalgic pain is reported by Tahmoush.[79] (*From* Melzack R: Psychological aspects of pain: Implications for neural blockade. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, ed 2. Philadelphia, Lippincott, 1988, p 845; with permission.)

Recently, several additional scoring procedures have been suggested.[7, 33, 50, 62] Hartman and Ainsworth[33] have proposed transforming the data into a pain ratio or fraction: the "pain ratio was calculated for each session by dividing post-session rating by the sum of the pre- and postsession ratings." Kremer et al[50] suggested dividing the sum of the obtained ranks within each dimension by the total possible score for a particular dimension, thus making differences between the sensory, affective, evaluative, and miscellaneous dimensions more interpretable.

A final form of computation[62] may be useful because it has been argued[7] that the McGill Pain Questionnaire fails to take into account the true relative intensity of verbal descriptors because the rank-order scoring system loses the precise intensity of the scale values obtained by Melzack and Torgerson.[65] For example, Figure 1 shows that the affective descriptors generally have higher scale values than the sensory words. This is clear when we consider the fact that the words "throbbing" and "vicious" receive a rank value of 4, but have scale values of 2.68 and 4.26, respectively, indicating that the latter descriptor implies considerably more pain intensity than the former. A simple technique was developed[62] to convert rank values to weighted rank values that more closely approximate the original scaled values obtained by Melzack and Torgerson.[65] Use of this procedure appears to provide enhanced sensitivity under certain circumstances.[62]

Usefulness of the McGill Pain Questionnaire

The most important requirement of a measure is that it be valid, reliable, consistent, and above all, useful. The McGill Pain Questionnaire appears to meet all of these requirements[6, 58, 73, 87] and provides a relatively rapid way of measuring subjective pain experience.[57] When administered to a patient by reading each subclass, it can be completed in about 5 minutes. It can also be filled out by the patient in a more leisurely way as a paper-and-pencil test, though the scores are somewhat different.[47]

Since its introduction in 1975, the McGill Pain Questionnaire has been used in over 100 studies of acute, chronic, and laboratory-produced pains. It has been translated into several languages and has also spawned the development of similar pain questionnaires in other languages. Pain questionnaires have appeared in Arabic,[32] Chinese,[34] Finnish,[45] German,[46, 71, 77] Dutch,[83, 85] Italian,[15, 54] and Spanish.[51]

Because pain is a private, personal experience, it is impossible for us to know precisely what someone else's pain feels like. No man can possibly know what it is like to have menstrual cramps or labor pain. Nor can a psychologically healthy person know what a psychotic patient is feeling when the patient says he or she has excruciating pain.[84] But the McGill Pain Questionnaire provides us with an insight into the qualities that are experienced. Recent studies indicate that each kind of pain is characterized by a distinctive constellation of words. There is a remarkable consistency in the choice of words by patients suffering the same or similar pain syndromes.[28, 30, 40, 63, 81]

Discriminative Capacity of the McGill Pain Questionnaire

One of the most exciting features of the McGill Pain Questionnaire is its potential value as an aid in the differential diagnosis between various pain syndromes.[16, 29, 35, 52, 64] The first study to demonstrate the discriminative capacity of the McGill Pain Questionnaire was carried out by Dubuisson and Melzack,[16] who administered the questionnaire to 95 patients suffering from one of eight known pain syndromes: postherpetic neuralgia, phantom limb pain, metastatic carcinoma, toothache, degenerative disk disease, rheumatoid arthritis or osteoarthritis, labor pain, and menstrual pain. A multiple-group discriminant analysis revealed that each type of pain is characterized by a distinctive constellation of verbal descriptors. Further, when the descriptor set for each patient was classified into one of the eight diagnostic categories, a correct classification was made in 77% of cases.

Descriptor patterns can also provide the basis for discriminating between two major types of low back pain. Some patients have clear physical causes such as degenerative disk disease, whereas others suffer low back pain even though no physical causes can be found. Using a modified version of the McGill Pain Questionnaire, Leavitt and Garron[52] found that patients with physical, organic, causes use distinctly different patterns of words from patients whose pain has no detectable cause and is labeled functional. A concordance of 87% was found between established medical diagnosis and classification based on the patients' choice of word patterns from the McGill Pain Questionnaire. Specific verbal descriptors of the McGill Pain Questionnaire have also been shown recently to discriminate between reversible and irreversible damage of the nerve fibers in a tooth.[29]

More recently, Melzack et al[64] provided further evidence of the discriminative capacity of the McGill Pain Questionnaire to differentiate between trigeminal neuralgia and atypical facial pain. Fifty-three patients were given a thorough neurologic examination that led to a diagnosis of either trigeminal neuralgia or atypical facial pain. Each patient rated his or her pain using the McGill Pain Questionnaire, and the scores were submitted to a discriminant analysis. Ninety-one percent of the patients were correctly classified using seven key descriptors. To determine how well the key descriptors were able to predict either diagnosis, the discriminant function derived from the 53 patients was applied to McGill Pain Questionnaire scores obtained from a second, independent validation sample of patients with trigeminal neuralgia or atypical facial pain. The results showed a correct prediction for 90% of the patients.

However, it is evident that the discriminative capacity of the McGill Pain Questionnaire has limits. High levels of anxiety and other psychological disturbance, which may produce high affective scores, may obscure the discriminative capacity.[48] Moreover, certain key words that discriminate among specific syndromes may be absent.[72] Nevertheless, it is clear that there are appreciable and quantifiable differences in the way various types of pain are described, and that patients with the same disease or pain syndrome tend to use remarkably similar words to communicate what they feel.

The Short-Form McGill Pain Questionnaire

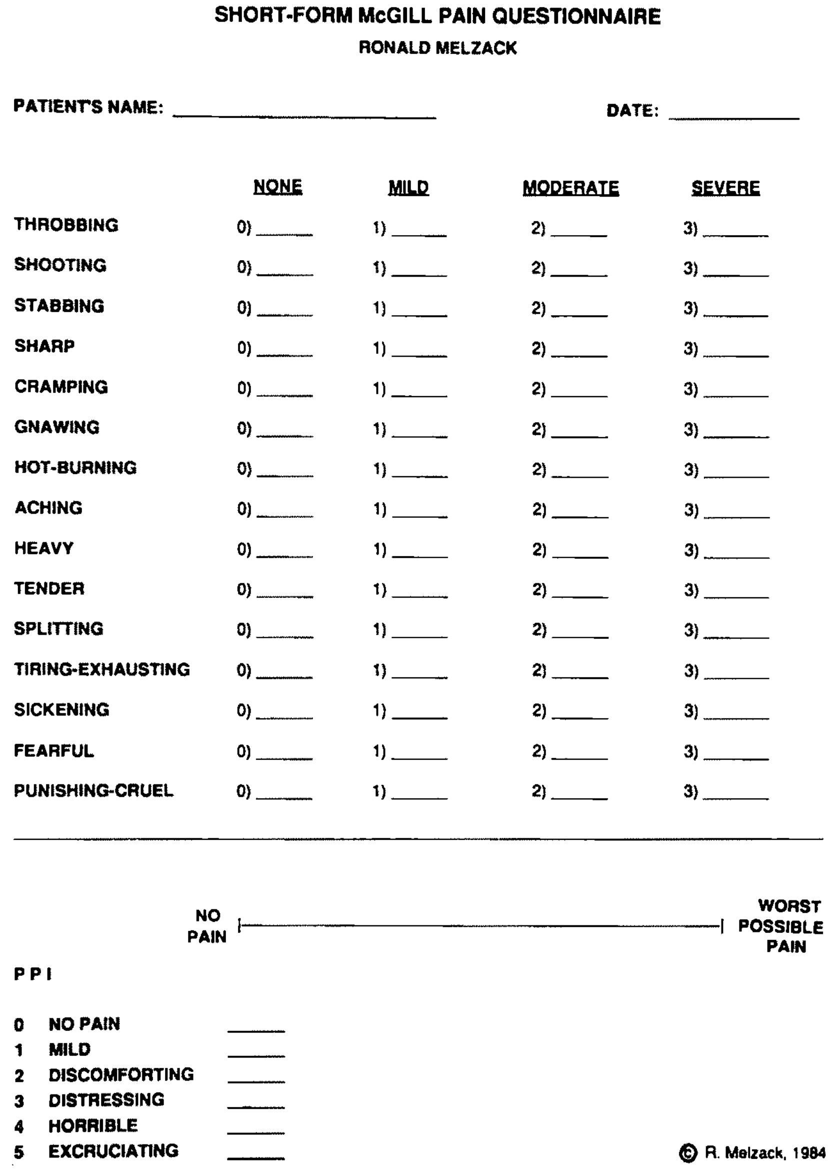
The short-form McGill Pain Questionnaire[60] (Fig. 4) was developed for use in specific research settings when the time to obtain information from patients is limited and when more information is desired than that provided by intensity measures such as the VAS or present pain intensity. The short-form McGill Pain Questionnaire consists of 15 representative words from the sensory (n = 11) and affective (n = 4) categories of the standard long form. The present pain intensity and a VAS are included to provide indices of overall pain intensity. The 15 descriptors making up the short-form McGill Pain Questionnaire were selected on the basis of their frequency of endorsement by patients with a variety of acute, intermittent, and chronic pains. An additional word, "splitting," was added because it was reported to be a key discriminative word for dental pain.[29] Each descriptor is ranked by the patient on an intensity scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

The short-form McGill Pain Questionnaire correlates very highly with the major pain rating indices (sensory, affective, and total) of the long-form and is sensitive to traditional clinical therapies—analgesic drugs, epidural blocks, and transcutaneous electrical nerve stimulation.[60] Preliminary results from a study designed to examine the qualities of pain experienced by patients in a physical rehabilitation hospital indicate that the sensory dimension of the short-form McGill Pain Questionnaire correlates highly with analgesic use among a subgroup of patients with high pain scores.[41] Furthermore, initial data[60] suggest that the short form may be capable of discriminating among different pain syndromes, which is an important property of the long form.

The Descriptor Differential Scale

Recently, simple but sophisticated psychophysical techniques have been applied to the development of pain measurement instruments used to assess clinical and experimentally induced pain.[19-21, 24, 31, 69] The psychophysical approach uses cross-modality matching procedures to determine the relative magnitudes of verbal descriptors of pain.[25]

The Descriptor Differential Scale was developed by Gracely et al[25] to remedy a number of deficiencies associated with existing pain measurement instruments. It was designed to reduce bias, assess the sensory intensity and "unpleasantness" (hedonic) dimensions of pain, and provide quantification by ratio-scaling procedures).[18] The Descriptor



SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: ____________________ **DATE:** __________

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) ____	1) ____	2) ____	3) ____
SHOOTING	0) ____	1) ____	2) ____	3) ____
STABBING	0) ____	1) ____	2) ____	3) ____
SHARP	0) ____	1) ____	2) ____	3) ____
CRAMPING	0) ____	1) ____	2) ____	3) ____
GNAWING	0) ____	1) ____	2) ____	3) ____
HOT-BURNING	0) ____	1) ____	2) ____	3) ____
ACHING	0) ____	1) ____	2) ____	3) ____
HEAVY	0) ____	1) ____	2) ____	3) ____
TENDER	0) ____	1) ____	2) ____	3) ____
SPLITTING	0) ____	1) ____	2) ____	3) ____
TIRING-EXHAUSTING	0) ____	1) ____	2) ____	3) ____
SICKENING	0) ____	1) ____	2) ____	3) ____
FEARFUL	0) ____	1) ____	2) ____	3) ____
PUNISHING-CRUEL	0) ____	1) ____	2) ____	3) ____

NO PAIN |————————————————| WORST POSSIBLE PAIN

P P I

0 NO PAIN ____
1 MILD ____
2 DISCOMFORTING ____
3 DISTRESSING ____
4 HORRIBLE ____
5 EXCRUCIATING ____

© R. Melzack, 1984

Figure 4. The short-form McGill Pain Questionnaire. Descriptors 1–11 represent the sensory dimension of pain experience, and 12–15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The PPI of the standard long-form McGill Pain Questionnaire and the visual analogue scale are also included to provide overall pain intensity scores. (*From* Melzack R: The short-form McGill Pain Questionnaire. Pain 30:191, 1987; with permission.)

Differential Scale consists of two forms that measure separately the sensory intensity and unpleasant qualities of pain. Each form consists of 12 verbal descriptors. Each descriptor is centered over a 21-point scale with a minus sign at the low end and a plus sign at the high end. The patients rate the magnitude of pain they are presently experiencing in relation to each descriptor by selecting 1 of the 21 possibilities associated with each descriptor. A separate score is obtained for the sensory intensity and unpleasantness dimensions by averaging the patient's choices on each 12-item form.

The Descriptor Differential Scale derived from cross-modality matching has been demonstrated to be differentially sensitive to pharmacologic interventions that alter the sensory or unpleasantness dimensions of pain.[23, 26, 27] Recent results point to the importance of using multidimensional measures of pain, with clear instructions to rate the sensory intensity and unpleasantness aspects of pain as opposed to the "painfulness" of the experience.[22] When used in conjunction with cross-modality matching techniques, the Descriptor Differential Scale has been shown to be a reliable and valid instrument with ratio-scale properties.[25, 26] More recently, Gracely and Kwilosz[24] assessed the psychometric properties of the Descriptor Differential Scale for use as a clinical pain measure.

Behavioral Approaches

Recent research into the development of behavioral measures of pain has produced a wide array of sophisticated observational techniques and rating scales designed to assess objective behaviors that accompany pain experience.[42] Techniques that have demonstrated high reliability and validity are especially useful for measuring pain in infants and preverbal children who lack language skills,[55, 56, 74] adults who have a poor command of language,[73] or when mental clouding or confusion limit the patient's ability to communicate meaningfully.[10] Under these circumstances, behavioral measures provide important information that is otherwise unavailable from patient self-report. Moreover, when administered in conjunction with a subjective, patient-rated measure, behavioral measures may provide a more complete picture of the total pain experience. However, behavioral measures of pain should not replace self-rated measures if the patient is capable of rating his or her subjective state and such administration is feasible.

The subjective experiences of pain and pain behaviors are, presumably, reflections of the same underlying neural processes. However, the complexity of the human brain indicates that, although experience and behavior are usually highly correlated, they are far from identical. One person may be stoic so that calm behavior belies his or her true subjective feelings. Another patient may seek sympathy (or analgesic medication or some other desirable goal) and in so doing exaggerate his or her complaints without also eliciting the behaviors that typically accompany pain complaints of that degree. Concordance between patients' self-ratings of pain and ratings of the same patients by nurses or other medically trained personnel may be modestly low,[8, 10, 53, 80, 82] but even in the presence of a significant correlation between physician and patient ratings of patient pain, physicians significantly underestimated the degree of pain the patients reported experiencing.[78] Craig and Prkachin[12, 13] have noted that when discordance is observed between nonverbal pain behavior and verbal pain complaint, the discrepancy often is resolved by disregarding the self-report. These studies point to the importance of obtaining multiple measures of pain and should keep us mindful that because pain is a subjective experience, the patient's self-report is the most valid measure of that experience.

Physiologic Approaches

Profound physiologic changes often accompany the experience of pain, especially if the injury or noxious stimulus is acute.[11] Physiologic correlates of pain may serve to elucidate mechanisms that underlie the experience and thus may provide clues that may lead to novel treatments.[6, 69] Physiologic correlates of pain experience that frequently are measured include heart rate, blood pressure, electrodermal activity, electromyography, and cortical evoked potentials. Despite high initial correlations between pain onset and changes in these physiologic responses, many habituate with time despite the persistence of pain.[19] In addition, these responses are not specific to the experience of pain per se, and occur under conditions of general arousal and stress. Recent studies that examined the general endocrine-metabolic stress response to surgical incision indicate that under certain conditions it is possible to dissociate different aspects of the stress response and pain.[43, 44] On the one hand, severe injury to a denervated limb produces a significant adrenocortical response.[44] On the other hand, use of general anesthesia clearly eliminates the conscious experience of pain in response to surgical incision, but does little to alter the subsequent rapid increase in plasma cortisol levels.[4, 9] These studies indicate, that, although there are many physiologic events that occur concurrently with the experience of pain, many appear to be general responses to stress and are not unique to pain.

SUMMARY

Pain is a personal, subjective experience influenced by cultural learning, the meaning of the situation, attention, and other psychological variables. Approaches to the measurement of pain include verbal and numeric self-rating scales, behavioral observation scales, and physiologic responses. The complex nature of the experience of pain suggests that measurements from these domains may not always show high concordance. But because pain is subjective, the patient's self-report provides the most valid measure of the experience. The VAS and the McGill Pain Questionnaire are probably the most frequently used self-rating instruments for the measurement of pain in clinical and research settings. The McGill Pain Questionnaire is designed to assess the multidimensional nature of pain experience and has been demonstrated to be a reliable, valid, and consistent measurement tool. A short-form McGill Pain Questionnaire is available for use in specific research settings when the time to obtain information from patients is limited and when more information than simply the intensity of pain is desired. Further development and refinement of pain measurement techniques will lead to increasingly accurate tools with greater predictive powers.

ACKNOWLEDGMENT

This work was supported by a fellowship from the Health Research Personnel Development Program of the Ontario Ministry of Health (JK) and Grant A7891 from the Natural Sciences and Engineering Research Council of Canada (RM). The results and conclusions derived herein are those of the authors, and no official endorsement by the Ontario Ministry of Health is intended or should be inferred.

References

1. Badner NH, Sandler AN, Koren G, et al: Lumbar epidural fentanyl infusions for post-thoracotomy patients: Analgesic, respiratory, and pharmacokinetic effects. J Cardiothorac Anesth 4:543, 1990
2. Beecher HK: Measurement of Subjective Responses. New York, Oxford University Press, 1959
3. Bélanger E, Melzack R, Lauzon P: Pain of first-trimester abortion: A study of psychosocial and medical predictors. Pain 36:339, 1989
4. Brandt MR, Kehlet H, Binder C, et al: Effect of epidural analgesia on the glucoregulatory endocrine response to surgery. Clin Endocrinol 5:107, 1976
5. Carlsson AM: Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 16:87, 1983
6. Chapman CR, Casey KL, Dubner R, et al: Pain measurement: An overview. Pain 22:1, 1985
7. Charter RA, Nehemkis AM: The language of pain intensity and complexity: New methods of scoring the McGill Pain Questionnaire. Percept Motor Skills 56:519, 1983
8. Choinière M, Melzack R, Girard N, et al: Comparisons between patients' and nurses' assessments of pain and medication efficacy in severe burn injuries. Pain 40:143, 1990
9. Christensen P, Brandt MR, Rem J, et al: Influence of extradural morphine on the adrenocortical and hyperglycaemic response to surgery. Br J Anaesth 54:24, 1982
10. Cleeland CS: Measurement of pain by subjective report. *In* Chapman CR, Loeser JD (eds): Issues in Pain Measurement (Advances in Pain Research and Therapy, vol 12). New York, Raven Press, 1989, p 391
11. Cousins M: Acute and postoperative pain. *In* Wall PD, Melzack R (eds): The Textbook of Pain, ed 2. Edinburgh, Churchill Livingstone, 1989, p 284
12. Craig KD: Clinical pain measurement from the perspective of the human laboratory. *In* Chapman CR, Loeser JD (eds): Issues in Pain Measurement (Advances in Pain Research and Therapy, vol 12). New York, Raven Press, 1989, p 433
13. Craig KD, Prkachin KM: Nonverbal measures of pain. *In* Melzack R (ed): Pain Measurement and Assessment. New York, Raven Press, 1983, p 173
14. Daley MD, Sandler AN, Turner KE, et al: A comparison of epidural and intramuscular morphine in patients following caesarean section. Anesthesiology 72:289, 1990

15. De Benedittis G, Massei R, Nobili R, et al: The Italian pain questionnaire. Pain 33:53, 1988
16. Dubuisson D, Melzack R: Classification of clinical pain descriptions by multiple group discriminant analysis. Exp Neurol 51:480, 1976
17. Ekblom A, Hansson P: Pain intensity measurements in patients with acute pain receiving afferent stimulation. J Neurol Neurosurg Psychiatr 51:481, 1988
18. Gracely RH: Pain language and ideal pain assessment. *In* Melzack R (ed): Pain Measurement and Assessment. New York, Raven Press, 1983, p 71
19. Gracely RH: Methods of testing pain mechanisms in normal man. *In* Wall PD, Melzack R (eds): The Textbook of Pain, ed 2. Edinburgh, Churchill Livingstone, 1989, p 257
20. Gracely RH: Pain Psychophysics. *In* Chapman CR, Loeser JD (eds): Issues in Pain Measurement (Advances in Pain Research and Therapy, vol 12). New York, Raven Press, 1989, p 211
21. Gracely RH, Dubner R: Pain assessment in humans—A reply to Hall. Pain 11:109, 1981
22. Gracely RH, Dubner R: Reliability and validity of verbal descriptor scales of painfulness. Pain 29:175, 1987
23. Gracely RH, Dubner R, McGrath PA: Fentanyl reduces the intensity of painful tooth pulp sensations: Controlling for detection of active drugs. Anesth Analg 61:751, 1982
24. Gracely RH, Kwilosz DM: The Descriptor Differential Scale: Applying psychophysical principles to clinical pain assessment. Pain 35:279, 1988
25. Gracely RH, McGrath PA, Dubner R: Ratio scales of sensory and affective verbal pain descriptors. Pain 5:5, 1978
26. Gracely RH, McGrath PA, Dubner R: Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: Manipulation of affect by diazepam. Pain 5:19, 1978
27. Gracely RH, McGrath PA, Dubner R: Narcotic analgesia: Fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science 203:1261, 1979
28. Graham C, Bond SS, Gerkovich MM, et al: Use of the McGill Pain Questionnaire in the assessment of cancer pain: Replicability and consistency. Pain 8:377, 1980
29. Grushka M, Sessle BJ: Applicability of the McGill Pain Questionnaire to the differentiation of 'toothache' pain. Pain 19:49, 1984
30. Grushka M, Sessle BJ, Miller R: Pain and personality profiles in burning mouth syndrome. Pain 28:155, 1987
31. Hall W: On "ratio scales of sensory and affective verbal pain descriptors." Pain 11:101, 1981
32. Harrison A: Arabic pain words. Pain 32:239, 1988
33. Hartman LM, Ainsworth KD: Self-regulation of chronic pain. Can J Psychiatr 25:38, 1980
34. Hui YL, Chen AC: Analysis of headache in a Chinese patient population. Ma Tsui Hsueh Tsa Chi 27:13, 1989
35. Hunter M: The headache scale: A new approach to the assessment of headache pain based on pain descriptions. Pain 16:361, 1983
36. Huskisson EC: Measurement of pain. Lancet 2:1127, 1974
37. Huskisson EC: Visual analogue scales. *In* Melzack R (ed): Pain Measurement and Assessment. New York, Raven Press, 1983, p 33
38. Jensen DM, Koroly P, Braver S: The measurement of clinical pain intensity: A comparison of six methods. Pain 27:117, 1986
39. Joyce CRB, Zutshi DW, Hrubes V, et al: Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 8:415, 1975
40. Katz J, Melzack R: Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. J Pain Symptom Management 6:73, 1991
41. Katz J, Vadnais M: A survey of pain and analgesic use in a physical rehabilitation hospital [abstract 30]. *In* Program and Abstracts of the 1990 Annual Meeting of the Canadian Pain Society, 1990
42. Keefe FJ: Behavioral measurement of pain. *In* Chapman CR, Loeser JD (eds): Issues in Pain Measurement (Advances in Pain Research and Therapy, vol 12). New York, Raven Press, 1989, p 405

43. Kehlet H: Pain relief and modification of the stress response. *In* Cousins MJ, Phillips GD (eds): Acute Pain Management. New York, Churchill Livingstone, 1986, p 49
44. Kehlet H: Modification of responses to surgery by neural blockade: Clinical implications. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, ed 2. Philadelphia, Lippincott, 1988, p 145
45. Ketovuori H, Pöntinen PJ: A pain vocabulary in Finnish—The Finnish pain questionnaire. Pain 11:247, 1981
46. Kiss I, Müller H, Abel M: The McGill Pain Questionnaire—German version. A study on cancer pain. Pain 29:195, 1987
47. Klepac RK, Dowling J, Rokke P, et al: Interview vs. paper-and-pencil administration of the McGill Pain Questionnaire. Pain 11:241, 1981
48. Kremer E, Atkinson JH: Pain language as a measure of affect in chronic pain patients. *In* Melzack R (ed): Pain Measurement and Assessment. New York, Raven Press, 1983, p 119
49. Kremer E, Atkinson JH, Ignelzi RJ: Measurement of pain: Patient preference does not confound pain measurement. Pain 10:241, 1981
50. Kremer EF, Atkinson JH, Ignelzi RJ: Pain measurement: The affective dimensional measure of the McGill Pain Questionnaire with a cancer pain population. Pain 12:153, 1982
51. Laheurta J, Smith BA, Martinez-Lage JL: An adaptation of the McGill Pain Questionnaire to the Spanish language. Schmerz 3:132, 1982
52. Leavitt F, Garron DC: Validity of a back pain classification scale for detecting psychological disturbance as measured by the MMPI. J Clin Psychol 36:186, 1980
53. Loeser JD: Pain relief and analgesia. *In* Chapman CR, Loeser JD (eds): Issues in Pain Measurement (Advances in Pain Research and Therapy, vol 12). New York, Raven Press, 1989, p 175
54. Maiani G, Sanavio E: Semantics of pain in Italy: The Italian version of the McGill Pain Questionnaire. Pain 22:399, 1985
55. McGrath PA: Pain in Children: Nature, Assessment, and Treatment. New York, Guilford, 1990
56. McGrath PJ, Unruh A: Pain in Children and Adolescents. Amsterdam, Elsevier, 1987
57. Melzack R: The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1:277, 1975
58. Melzack R: Pain Measurement and Assessment. New York, Raven Press, 1983
59. Melzack R: Psychological aspects of pain: Implications for neural blockade. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, ed 2. Philadelphia, Lippincott, 1988, p 845
60. Melzack R: The short-form McGill Pain Questionnaire. Pain 30:191, 1987
61. Melzack R, Casey KL: Sensory, motivational, and central control determinants of pain: A new conceptual model. *In* Kenshalo D (ed): The Skin Senses. Springfield, IL: CC Thomas, 1968, p 423
62. Melzack R, Katz J, Jeans ME: The role of compensation in chronic pain: Analysis using a new method of scoring the McGill Pain Questionnaire. Pain 23:101, 1985
63. Melzack R, Taenzer P, Feldman P, et al: Labour is still painful after prepared childbirth training. Can Med Assoc J 125:357, 1981
64. Melzack R, Terrence C, Fromm G, et al: Trigeminal neuralgia and atypical facial pain: Use of the McGill Pain Questionnaire for discrimination and diagnosis. Pain 27:297, 1986
65. Melzack R, Torgerson WS: On the language of pain. Anesthesiology 34:50, 1971
66. Melzack R, Wall PD: The Challenge of Pain, ed 2. London, Penguin Books, 1988
67. Melzack R, Wall PD, Ty TC: Acute pain in an emergency clinic: Latency of onset and descriptor patterns. Pain 14:33, 1982
68. Ohnhaus EE, Adler R: Methodological problems in the measurement of pain: A comparison between the verbal rating scale and the visual analogue scale. Pain 1:374, 1975
69. Price DD: Psychological and Neural Mechanisms of Pain. New York, Raven Press, 1988, p 18
70. Price DD, McGrath PA, Rafii A, et al: The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 17:45, 1983

71. Radvila A, Adler RH, Galeazzi RL, et al: The development of a German language (Berne) pain questionnaire and its application in a situation causing acute pain. Pain 28:185, 1987
72. Reading AE: An analysis of the language of pain in chronic and acute patient groups. Pain 23:185, 1982
73. Reading AE: Testing pain mechanisms in persons in pain. *In* Wall PD, Melzack R (eds): The Textbook of Pain, ed 2. Edinburgh, Churchill Livingstone, 1989, p 269
74. Ross DM, Ross SA: Childhood Pain: Current Issues, Research, and Management. Baltimore, Urban & Schwarzenberg, 1988
75. Scott J, Huskisson EC: Vertical or horizontal visual analogue scales. Ann Rheum Dis 38:560, 1979
76. Sriwatanakul K, Kelvie W, Lasagna L, et al: Studies with different types of visual analog scales for measurement of pain. Clin Pharmacol Ther 34:234, 1983
77. Stein C, Mendl G: The German counterpart to McGill Pain Questionnaire. Pain 32:251, 1988
78. Sutherland JE, Wesley RM, Cole PM, et al: Differences and similarities between patient and physician perceptions of patient pain. Fam Med 20:343, 1988
79. Tahmoush AJ: Causalgia: Redefinition as a clinical pain syndrome. Pain 10:187, 1981
80. Teske K, Daut RL, Cleeland CS: Relationships between nurses' observations and patients' self-reports of pain. Pain 16:289, 1983
81. Van Buren J, Kleinknecht R: An evaluation of the McGill Pain Questionnaire for use in dental pain assessment. Pain 6:23, 1979
82. Van der Does, AJW: Patients' and nurses' ratings of pain and anxiety during burn wound care. Pain 39:95, 1989
83. Vanderiet K, Adriaensen H, Carton H, et al: The McGill Pain Questionnaire constructed for the Dutch language (MPQ-DV). Preliminary data concerning reliability and validity. Pain 30:395, 1987
84. Veilleux S, Melzack R: Pain in psychotic patients. Exp Neurol 52:535, 1976
85. Verkes RJ, Van der Kloot WA, Van der Meij J: The perceived structure of 176 pain descriptive words. Pain 38:219, 1989
86. Whiting WC, Sandler AN, Lau LC, et al: Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. Anesthesiology 69:36, 1988
87. Wilke DJ, Savedra MC, Holzemer WL, et al: Use of the McGill Pain Questionnaire to measure pain: A meta-analysis. Nurs Res 39:36, 1990

Address reprint requests to

Joel Katz, PhD
Department of Psychology
The Toronto Hospital
Toronto General Division
200 Elizabeth Street
CW2-306
Toronto, Ontario
Canada M5G 2C4

PHYSIOLOGIC CONSEQUENCES OF TISSUE INJURY AND ACUTE PAIN

Terence J. Coderre, MSc, PhD

Until recently, the predominant view of the pain pathway was that of a static, passive relay system that transmitted information about a noxious stimulus to the brain. Recently, however, evidence is accumulating that suggests that the pain pathway is an active, dynamic system, which both responds and contributes to pain sensations in a complex manner. Tissue injury or acute pain produces profound effects both in the peripheral and central nervous systems (CNS) that alter sensitivity to subsequent stimuli. While the pain system normally acts in a useful manner to alert the individual to actual or potential tissue damage, a pathologic pain state develops following tissue injury or sustained acute pain. In the absence of tissue injury, the pain system provides a highly reliable stimulus-response function, in which the intensity of the noxious stimulus can be predicted fairly accurately by the sensory response. In pathologic pain that follows injury, there is a reduction in pain threshold (allodynia), an increased response to noxious stimuli (hyperalgesia), an increase in the duration of response to brief stimulation (persistent pain), and a spread of pain and hyperalgesia to uninjured tissue (referred pain and hyperalgesia). These pathologic changes are dependent on injury-induced alterations within both the peripheral and CNS.

The present article reviews the injury-induced changes in peripheral and central nervous function and their effects on pain sensitivity. Through a better understanding of the changes in nervous system function that underlie pathologic pain, it is hoped that it will be possible

---

From the Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Département de Médecine, Université de Montréal, and Department of Psychology, McGill University, Montreal, Quebec, Canada

to retard the development of chronic pain or pain that persists past the normal time of tissue healing.

PERIPHERAL EFFECTS

Following an injury to cutaneous tissue, there are a series of defensive reactions that serve as a protective mechanism against further skin injury. Lewis[92] described a "triple response" of injured skin: a local reddening at the site of injury, followed by a wheal characterized by swelling, tenderness, and redness just around the injury, and a subsequent flare or spreading of redness to surrounding tissue. These reactions demonstrate the four classic signs of inflammation: redness, heat, swelling, and pain. The redness and heat are caused by a dilation of blood vessels and by the large amounts of warm blood close to the skin surface. Swelling or edema is due to plasma extravasation (the leakage of fluids) from the blood vessels into the tissue. Pain is caused by a direct activation of peripheral nociceptors by the noxious stimulus, as well as by stimulation from toxic substances released in response to the injury.

Along with inflammation, the cutaneous tissue becomes hyperalgesic or more sensitive to cutaneous stimulation. Pain responses to both mechanical and thermal stimuli are enhanced. The hyperalgesia is present not only at the site of injury, but also spreads to surrounding uninjured tissue. The hyperalgesia that follows a tissue injury may develop as a result of several different mechanisms. First, the tissue injury results in an increased responsiveness of nociceptors at the site of injury (nociceptor sensitization). Second, there is a release/production and diffusion of pain-producing substances that activate or sensitize nociceptors in injured and uninjured tissue. Third, vasodilatory substances are released from the peripheral terminals of afferents activated by the injury, mediating the spread of inflammation and hyperalgesia into uninjured tissue (neurogenic inflammation). The properties associated with these three mechanisms are discussed in detail in the following sections.

Nociceptor Sensitization

Following tissue injury there is an increase in the excitability of primary afferent nociceptors. Nociceptor sensitization is reflected by one or more of the following: a decrease in threshold, an increase in impulse frequency to the same stimulus (Fig. 1), a decrease in latency of the first impulse, an afterdischarge following extended or intense stimulation, and the appearance of spontaneous firing.[8] Repeated heat stimulation produces sensitization that develops within 1 minute and lasts for hours.[110] Following heating of the skin, sensitization to further heat stimuli has been demonstrated in C-fiber polymodal nociceptive units in the rat,[95] rabbit,[111] cat,[9] monkey,[8] and humans.[128]

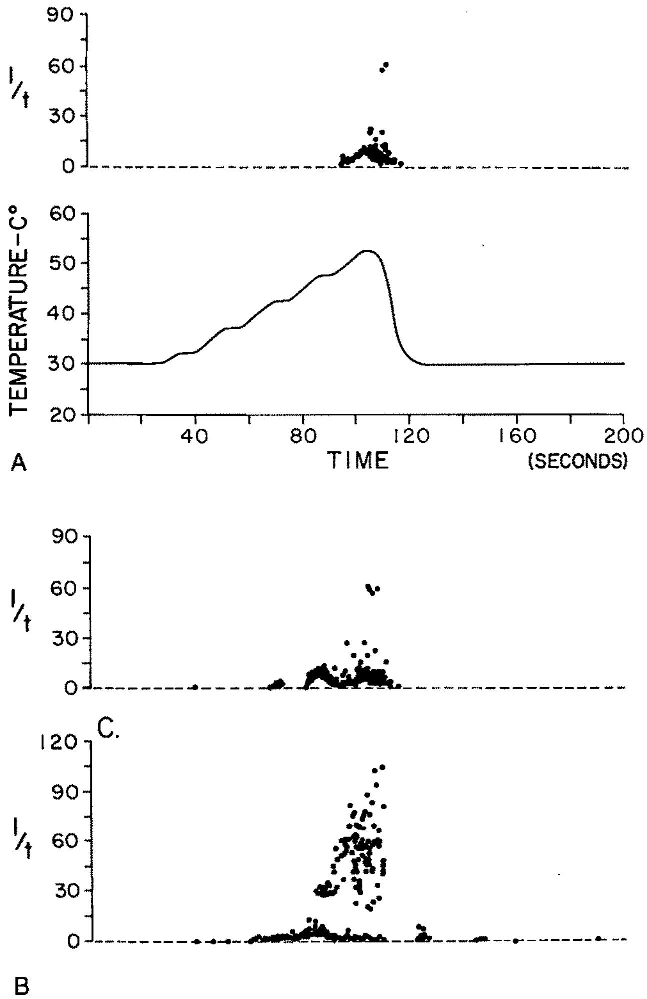


Figure 1. Response of a monkey C-fiber polymodal nociceptor to repeated noxious heating of the receptive field by means of a small contact thermode. The lower graph in A shows the thermode temperature near the skin interface during a cycle of heat pulses of increasing intensity. The upper graph in *A*, and the graphs in *B* and *C*, plot the receptor's discharge to the first, third, and fifth heating cycle, respectively. (*From* Kumazawa T, Perl ER: Primate cutaneous sensory units with unmyelinated (c) afferent fibers. J Neurophysiol 6:1325, 1977; with permission.)

Sensitization after heat injury has also been found in the heat responses of A delta fiber, high-threshold mechanoreceptor units in the rabbit, cat,[49] and monkey,[103] as well as in the paradoxical responses of cold receptors in monkeys.[42] Although mechanical injury stimuli have not been used in the study of nociceptor sensitization in mammals, cutaneous nociceptors in the frog have been found to be sensitized to mechanical stimulation following injury of the skin by scraping.[44] It has also been shown that both polymodal nociceptors[9] and high-threshold mechanoreceptors[49] do not become sensitized to mechanical stimuli following heat injury, although this has recently been questioned.[15]

Recent studies have attempted to demonstrate a correlation between nociceptor sensitization and reports of hyperalgesia following a cutaneous injury. Initially this was performed by comparing magnitude estimations of hyperalgesia in humans with neurophysiologic recordings in nerve fibers of monkeys[85, 103] (Fig. 2). More recent studies have examined the correlation between human sensory judgements and evoked neural responses in the same subjects using percutaneous recording techniques.[128] The results of these studies have been controversial. While Meyer and Campbell[103] reported that hyperalgesia is associated with a sensitization of A fibers and a desensitization of C fibers, LaMotte et al[85] and Torebjörk et al[128] suggested that hyperalgesia is related to a sensitization of C fibers and not A fibers. This discrepancy may depend on either the type of skin injured (hairy versus glaborous) or the intensity of the stimulus producing the injury.

Pain-Producing Substances

Evidence suggests that nociceptor sensitization and hyperalgesia at the site of injury are partly mediated by the release of toxic substances

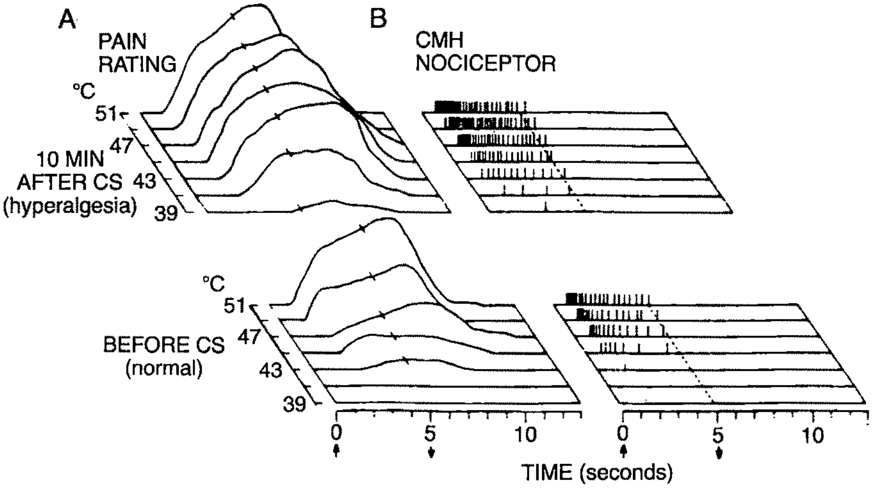


Figure 2. Magnitude ratings of pain by a human subject and evoked responses of a C-fiber mechanoheat (CMH) nociceptor in the monkey during heat stimulations (between 39–51°C) of the hairy skin before and 10 min after a mild injury by heat (a 50°C stimulus of 100 sec duration). The upward arrow marks the onset of the stimulus, while the downward arrow and horizontal tick marks denote the termination of the stimulus. *A* Magnitude ratings of pain: Hyperalgesia had developed by 10 min, as indicated by a lowering of pain threshold from 43°C to 39°C and enhanced ratings of suprathreshold stimuli. *B* Responses of a CMH nociceptor: Each vertical mark represents a single action potential. By 10 minutes after the injury, the nociceptor had become sensitized, as evidenced by a lowering of threshold and enhanced frequency of discharge to suprathreshold stimuli. (*From* LaMotte RH, Thalhammer JG, Robinson CJ, et al: Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: A comparison of neural events in monkey with sensory judgment in human. J Neurophysiol 50:1–25, 1983; with permission.)

from cells damaged by the injury. Chapman et al[18] found that perfusate taken from the subcutaneous space of injured skin produces hyperalgesia in uninjured skin. Exposure to severe or prolonged noxious stimulation results in tissue damage. The damage is reflected by a destruction of cells, as well as nerve endings, at the site of injury. The chemicals potassium (K^+) and adenosine triphosphate, which are contained in the cells of tissue, are released following injury.[73, 78] The release of K^+ and adenosine triphosphate causes a sensitization of nerve endings[51, 74] and likely produces pain sensations because each chemical has been found to produce pain when applied to the exposed base of a blister.[78] Following tissue injury there is also a local release of serotonin and bradykinin from blood,[41, 116] as well as histamine from damaged mast cells.[115] Histamine is reported to sensitize C-fiber nociceptive units[50] and produces pain following intradermal injection.[12] Serotonin causes a sensitization of cutaneous nociceptors[7] and pain sensations when applied to a blister base.[78] Like histamine and serotonin, bradykinin produces an excitation of nociceptors[7, 9] and is painful when injected into the skin.[59]

Tissue damage is also followed by the production and accumulation of arachidonic acid metabolites in inflammatory perfusate.[3] The cycloxygenase products of arachidonic acid metabolism, prostaglandins, cause a sensitization of C-fiber nociceptors[62] and produce pain following high-concentration intradermal[45] and intramuscular[76] injections. Lower concentrations do not cause overt pain, but do cause hyperalgesia when administered intradermally[75] or subcutaneously.[45] It has been suggested that prostaglandins facilitate inflammation, the sensitization of nociceptors, and hyperalgesia by enhancing the effects of the other previously mentioned substances that are released in inflammatory perfusate.[74] Recently, it has been demonstrated that the lipoxygenase products of arachadonic metabolism also sensitize nociceptors[98, 130] and produce hyperalgesia[91] on intradermal injection.

Neurogenic Inflammation

Lewis[93] noted that the spread of hyperalgesia following cutaneous tissue injury coincided with the development of a flare or reddening of the skin surrounding the injury. It has long been known that the development of a flare is associated with vasodilatation that is dependent on neural mechanisms. First, a flare response can be elicited by antidromic stimulation of a peripheral nerve.[56] Second, the flare response to noxious skin stimulation is absent in denervated regions of skin.[105] Third, inflammatory responses to noxious stimulation are diminished by an injection of a local anesthetic to the area.[122] It is also known that flare responses are mediated by peripheral mechanisms independent of the CNS. Bayliss[6] demonstrated that a flare response could be generated following stimulation of the peripheral end of a transected dorsal root. Bruce[13] argued that sensory fibers activated antidromic inflammatory responses and suggested that they were the result of an axon reflex similar to that described by Langley and Anderson[86] in preganglionic sympathetic fibers.

The relationship between reflex vasodilatation and the painfulness of the injury necessary to produce it also led researchers to conclude that axon reflexes were produced in fibers that transmit pain. Celander and Folkow[16] studied vasodilatation after heating of the skin and noted that although a 55°C stimulus produced an axon reflex response, a 40°C stimulus did not. Gasser[54] demonstrated that dorsal root stimulation must be at C-fiber strength to produce vasodilatation. Recently, Kenins[80] demonstrated that neurogenic inflammation can be produced in the rat hind leg by antidromic stimulation of C-polymodal nociceptive fibers, but not by stimulation of C low-threshold mechanosensitive or warm sensitive fibers. It is now assumed that neurogenic inflammation typically occurs when stimuli, strong enough to elicit pain, generate impulses in nociceptive C fibers. The impulses travel not only centrally to signal pain, but also propagate antidromically, in the branches of the nerve fibers that innervate blood vessels, and produce neurogenic inflammation.

It seems very likely that the spread of hyperalgesia is, in part, mediated by the same process. Bilisoly et al[10] have shown that pain sensitivity in the skin around an injection of histamine increases during the phase of active vasodilatation that produces a flare. Lewis[93] proposed that, in response to an injury, a neurogenic system in the periphery produces hyperalgesia while mediating elements of skin defense such as inflammation. His hypothesis was based on several observations. First, he noted that the spread of hyperalgesia around a skin injury could be delayed by a local injection of procaine administered before the injury. Second, he could produce hyperalgesia by antidromically stimulating cutaneous nerves. Third, like hyperalgesia following an injury, hyperalgesia produced by antidromic stimulation could be delayed by local anesthesia. In addition, if the nerve was stimulated distal to a procaine block, hyperalgesia would develop normally after the nerve recovered from the block. However, if the nerve stimulation was central to the block, hyperalgesia never developed. These findings strongly suggest that the spread of hyperalgesia is mediated by peripheral nerves.

Support for Lewis's mechanism of spreading hyperalgesia comes from several sources. Perl et al[111] showed that an extensive skin injury produced a sensitization of C-fiber polymodal units whose receptive fields were removed from the injured region. Fitzgerald[48] recorded activity in C-fiber nociceptive units in the skin near an injury and found that nociceptors in the uninjured tissue were more sensitive to heat following an injury than when there was no injury. The spread of the effect of the injury was induced by nerve impulses, because a local injection of lidocaine anesthetic blocked the spread of sensitization. Fitzgerald also found that there was a spread of nociceptor sensitization following antidromic stimulation of the rabbit sural nerve at C-fiber strength. The effect was independent of the CNS because it occurred even when the nerve was cut central to the stimulation point. Chahl and Ladd[17] demonstrated that antidromic stimulation of the rat saphenous nerve produced inflammation and an increased excitability in sensory nerve fibers when the stimulation was of C-fiber, but not A-fiber, strength.

Although Lewis[93] was incorrect in attributing the spread of hyperalgesia to axon reflexes in a set of undiscovered "nocifensor" nerves (rather than afferent nerves), he was correct in suggesting that peripheral nerves mediated the spread of hyperalgesia by liberating pain-producing or pain-enhancing substances into the uninjured skin around an injury. Lewis and Marvin[94] presented evidence that inflammation is mediated by such a substance by showing that the duration of a flare can be increased by occlusion of the blood to the area. Chapman et al[18] noted that during the period of active vasodilatation a substance is released into the subcutaneous perfusate. Because the substance was not released during plasma extravasation, they concluded that it is a mediator of vasodilatation and not just released as a consequence of inflammation.

Recent evidence suggests that the mediator of neurogenic inflammation is substance P. First, substance P is found in skin[67] and in the peripheral terminals of unmyelinated sensory fibers.[33] Second, peripheral nerve stimulation causes a release of substance P from its nerve terminals.[109] Third, substance P injections produce both vasodilatation and plasma extravasation.[53] Fourth, substance P antagonists block the vasodilatation and plasma extravasation produced by injury,[68] antidromic nerve stimulation,[90] and substance P injections.[117] Fifth, substance P causes hyperalgesia in mice following subcutaneous injection,[108] and produces pain in humans when applied to a blister base.[4] Sixth, substance P is found to be elevated in the peripheral nerves of animals with inflammatory pain due to adjuvant-induced arthritis.[88] Seventh, substance P stimulates sensory nerve endings when perfused into the rabbit ear.[87] Eight, along with the flare responses, substance P in peripheral nerves is reduced in the region innervated by the nerve following transection.[2]

It has been suggested that substance P may produce its peripheral effects through an interaction with histamine from mast cells. It has been shown that substance P causes a release of histamine from rat peritoneal mast cells[72] and in human mast cells.[60] Furthermore, only substance P analogues that release histamine from mast cells produce a flare response in human skin.[46] Also, H_1-histamine antagonists prevent the flare response to infusion of substance P or antidromic stimulation.[52, 90]

Recently, Lembeck and Gamse[89] have proposed a model for peripheral mechanisms of inflammation and the spread of hyperalgesia that describes the role of many of the substances discussed so far in this review. According to this model (Fig. 3), tissue damage following injury causes a release of potassium (K^+) from damaged cells, bradykinin from blood, and histamine from mast cells. Together, these substances stimulate nociceptors and induce the production of prostaglandins.

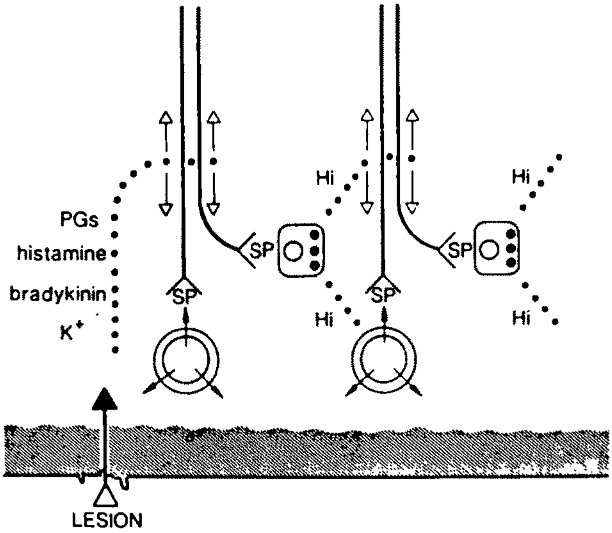


Figure 3. Suggested mechanism underlying the axon response (for explanation, see text). Hi, histamine; K^+, potassium; PGs, prostaglandins; SP, substance P. (*From* Lembeck F, Gamse R: Substance P in peripheral sensory processes. *In* Porter R, O'Connor M (eds): Substance P in the Nervous System [Ciba Foundation Symposium 91]. London, Ciba Foundation, 1982, p 35; with permission.)

Prostaglandins both trigger inflammation and facilitate the stimulation of nociceptors. The stimulation of nociceptors causes the release of substance P from its nerve terminals, and as the level of stimulation increases, pain signals are generated. When released from peripheral terminals, substance P induces vasodilatation, producing a flare response, as well as causing a further release of histamine from adjacent mast cells. The release of further histamine results in the initiation of a repetition of the cycle in adjacent neurons, leading to increasing inflammation and the spread of hyperalgesia to uninjured tissue.[89] Recent evidence suggests that in articular tissue, this mechanism may also include an action of histamine from mast cells on sympathetic postganglionic neurons,[22] which produce further inflammation by releasing prostaglandins.[57]

CENTRAL EFFECTS

Recent evidence suggests that in addition to the effects of tissue injury or noxious stimulation on primary afferent neurons, there are also effects within the CNS. A central mechanism of spreading hyperalgesia proposed by Sturge[123] and Hardy et al[63] has been supported by reports that cutaneous hyperalgesia spreads well beyond the area of nociceptor sensitization. Thalhammer and LaMotte[126] found that a heat injury in one half of a cutaneous nociceptor's receptive field did not produce heat sensitization in the other half, despite the fact that hyperalgesia spread into this area. Typically, nociceptor sensitization associated with injury is restricted to about 5 to 10 mm of the site of injury,[15, 48] whereas cutaneous hyperalgesia spreads as far as 10 to 20 cm beyond the site of injury.[63]

The spread of hyperalgesia as well as long-term CNS effects of peripheral tissue injury occur, in part, as a result of central sensitization. Central sensitization is reflected by various phenomena described, including the wind-up, sensitization, and expansion of the receptive fields of dorsal horn neurons, and an increased excitability of flexion reflexes. There are also various animal models of persistent pain that reflect changes in central neural function, because pain persists even after inputs from the injured region are blocked. This central sensitization, and the neuroplasticity it reflects, is dependent on neurochemical, cellular, and molecular events in the CNS that are triggered by peripheral tissue injury.

Wind-Up and Sensitization of Dorsal Horn Neurons

Coincident with spreading hyperalgesia following peripheral tissue injury is the sensitization of spinal cord dorsal horn neurons. Dorsal horn neurons fire with increasing frequency in response to repeated applications of the same noxious heat stimulus.[110] The sensitization of dorsal horn neurons occurs after tissue injury[81] or stimulation of C-fiber afferent nerves[20, 32] (Fig. 4B). An injury or noxious stimulation may also induce a hyperexcitable state in dorsal horn neurons. In such cases, repeated noxious peripheral input sequentially increases dorsal horn activity, resulting in a prolonged discharge or wind-up of the cell, lasting from seconds to minutes poststimulation.[101]

Receptive Field Expansion

In addition to the sensitization and prolonged excitation of dorsal horn cells, noxious stimulation associated with tissue injury also produces an expansion of the receptive fields of dorsal horn neurons. Neurons in the dorsal horn of the spinal cord with receptive fields adjacent to a cutaneous heat injury expand their receptive fields to incorporate the site of injury.[100] Similar receptive field expansions have been observed following chemical,[66] inflammatory,[70] and nerve[38] injuries, as well as C-fiber nerve stimulation[32] (Fig. 4A). In fact, even surgical incisions associated with a hind limb operation are capable of producing receptive field expansions in dorsal horn neurons.[66] In the case of nerve injury, sensory disturbances associated with the injury have been found to be closely associated with such alterations in dorsal horn function. Markus et al[97] have demonstrated that the development of hypersensitivity in a rat's hind paw following sciatic nerve section occurs

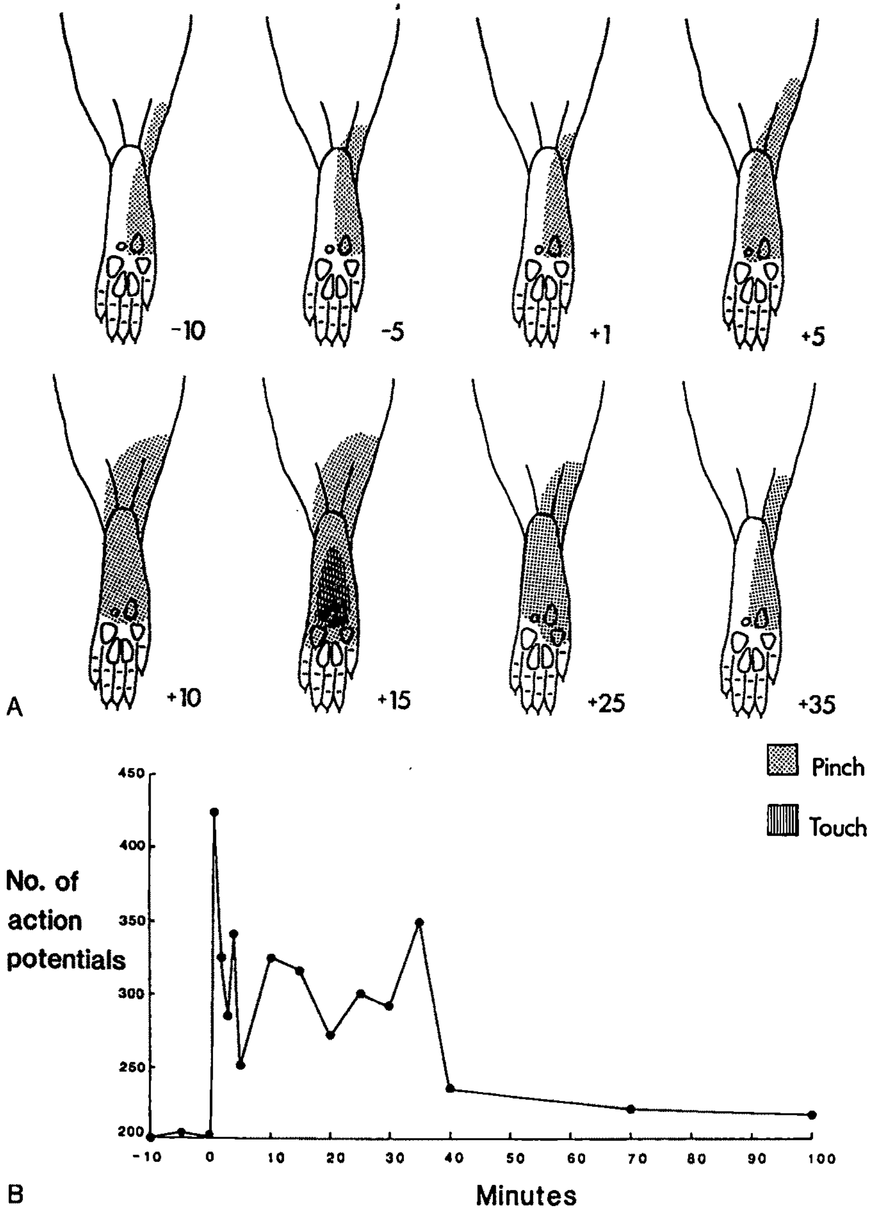


Figure 4. *A,* Expansion of the pinch receptive field of a dorsal horn neuron following a C-fiber-strength conditioning stimulus at time 0 to the gastrocnemius-soleus nerve (1 Hz, 20 sec). Note that 15 min after the conditioning stimulus the neuron begins to respond to a low-intensity mechanical stimulus (touch). *B,* Change in the total number of action potentials in a neuron evoked by a standard pinch applied for 3 sec to the medial edge of the foot following the gastrocnemius-soleus conditioning stimulus at time 0. (*From* Cook AJ, Woolf CJ, Wall PD, et al: Dynamic receptive field plasticity in rat spinal dorsal horn following C-primary afferent input. Nature 325:151, 1987; with permission.)

concurrently with the expansion of the saphenous nerve's somatotopic projection in the spinal cord.

Alterations in Flexion Reflexes

In addition to its role in enhancing pain transmission to central structures, the sensitization of spinal dorsal horn neurons also leads to an enhancement of spinal reflexes, including the flexion reflex. Woolf[135] demonstrated that localized thermal and chemical injuries cause reductions in flexion reflex thresholds to noxious mechanical and thermal stimulation in the limb contralateral as well as ipsilateral to the injury. Cutaneous,[134] as well as deep tissue,[136] injury and noxious electrical stimulation of cutaneous and muscle[32, 130] afferents, also produce an increase in the excitability of the ipsilateral and contralateral flexor efferent nerves in response to noxious mechanical stimulation of the hind paw. The spread of hyperalgesia or flexor efferent excitability to the contralateral side implies that spinal sensitization is involved. Furthermore, because the increased excitability in the contralateral flexor efferent is maintained even after inputs from the injured paw are blocked by local anesthesia, the results suggest that central, and not peripheral, changes underlie this effect. In this way, cutaneous hyperalgesia after injury may depend on central sensitization that is produced by, but does not need to be maintained by, inputs from a peripheral injury. In our laboratory, we have demonstrated that the spread of hyperalgesia (i.e., decreased paw-withdrawal latencies from 47°C water) to the hind paw contralateral to a thermal injury is unaffected by either deafferentation or anesthetic blocks of the injured hind paw following the injury, but is prevented if deafferentation or anesthetic block of the injured hind paw precedes the injury.[26, 27] These data provide further evidence that peripheral injury can produce central changes that are maintained even after the inputs from the injury are removed.

Animal Models of Persistent Pain

Recent evidence suggests that in addition to reflex nociceptive measures, animal models of persistent pain are also influenced by central sensitization. In neuropathic pain models, there is increasing evidence that the level of noxious input, present at the time of the initial pain-inducing injury, plays a significant role in determining subsequent pain experience. Deafferentation by peripheral neurectomy or dorsal rhizotomy in rodents is followed by self-mutilation, or autotomy, in which animals bite and scratch the insensate paw to the point of amputation. There is strong evidence that this autotomy behavior is produced by ongoing pain or dysesthesia, associated with increased neuronal activity, which is referred to the anesthetic region.[11, 24] Studies in our laboratory demonstrate that subsequent autotomy behavior is dramatically affected by alterations in the level of noxious inputs present at the time of nerve injury or section. These studies have shown that noxious chemical,[23, 36] thermal,[26–28] and electrical nerve[77] stimulation, before nerve sections, significantly increases the severity of autotomy following neurectomy or rhizotomy. These findings suggest that the prior injury is capable of producing central changes that influence pain behavior, after nerve sections, at a time when inputs from the injured region are no longer capable of transmitting their message centrally.

In contrast to the effect of increasing noxious inputs at the time of nerve injury, reducing or eliminating the afferent barrage induced by nerve section produces a dramatic reduction in deafferentation pain. When the afferent barrage induced by nerve cuts is blocked by treating the cut nerves with local anesthetics before sectioning them, there is a significant reduction in the incidence and severity of autotomy in these rats.[58] Similarly, in human amputees, phantom limb pain for at least 12 months after amputation is significantly reduced in patients given an epidural block with bupivacaine and morphine to eliminate preamputation pain before amputation surgery.[5]

In addition to neuropathic pain, persistent pain after formalin-induced tissue injury also is influenced by central sensitization. A subcutaneous injection of dilute formalin produces a biphasic nociceptive response in rats, with an early phase of intense pain occurring in the first few minutes, a quiet intermediate period of little or no pain lasting 5 to 10 minutes, and a later persistent or tonic phase of moderate pain expressed about 15 to 60 minutes after formalin injection.[43] The nociceptive response to subcutaneous formalin is matched by a similar biphasic increase in the activity of dorsal horn neurons after formalin injection.[40, 61] Dickenson and Sullivan[40] have demonstrated that the intrathecal administration of the μ-opiate agonist Tyr-D-AlaGlyMe-PheGly-ol significantly inhibits the prolonged increase in dorsal horn activity produced by subcutaneous formalin injection. However, this inhibition occurred only if the drug was given before the formalin injection, and not if was given 2 minutes after the injection. These results imply that the dorsal horn activity associated with the late phase of the formalin response depends on spinal activation during the early phase after formalin injection.

In our own studies, we have examined the contribution of central sensitization to persistent pain in the formalin test by assessing the effects of anesthetic agents given in local subcutaneous injections or intrathecally, either before or after the early phase of the formalin response, on subsequent nociceptive behavior during the late phase of the formalin test.[31] Our results demonstrated that the persistent nociceptive responses in the late phase (30–60 minutes after formalin) were not eliminated by complete anesthetic blockade of the formalin-injected area at the time of testing (bupivacaine given 5 minutes after formalin injection and again 5 minutes before testing), but were virtually eliminated if a local anesthetic block of the area was also present at the time of formalin injection (bupivacaine given 5 minutes before formalin injection and again 5 minutes before testing). Furthermore, late-phase nociceptive responses were significantly reduced by spinal anesthesia at the time of formalin injection (intrathecal lidocaine given 5 minutes before formalin injection), but not by spinal anesthesia administered after formalin injection (intrathecal lidocaine given 5 minutes after formalin injection), i.e., after the early phase had already occurred.[31] These results suggest that central neural changes, which occur during the early phase of the formalin test, are essential for the development of the later persistent pain phase of the formalin test.

Neurochemical Mediators of Central Sensitization

Evidence suggests that C-fiber neuropeptides are involved in triggering central sensitization. First, the increased excitability in flexor efferents, induced either by C-fiber strength electrical stimulation or by the application of chemical irritants, is blocked by pretreatment of the affected nerves with the C-fiber neurotoxin capsaicin.[137] Second, the application of small combined doses of the C-fiber neuropeptides substance P and calcitonin gene-related peptide or calcitonin gene-related peptide and somatostatin produce a prolonged enhancement in the excitability of the flexion reflex.[132, 138] Third, hyperalgesia that develops in the hind limb contralateral to a thermal injury is mimicked by intrathecal treatment with the C-fiber neuropeptides substance P and neurokinin A and is reversed by the substance P antagonist D-Arg^1, Pro^2, D-Phe^2, D-His^9-substance P[25]. Fourth, the repetitive stimulation of dorsal roots elicits a slow depolarization in dorsal horn neurons that is mimicked by the application of substance P, vasoactive intestinal polypeptide or cholecystokinin, and blocked by substance P antagonists or capsaicin applied to the tissue bath.[129] Fifth, a subcutaneous injection of formalin, which we have shown produces a persistent pain response associated with central sensitization (see previous section), evokes an immediate, intense barrage of C-fiber afferent activity[64] and elicits an increase in substance P in the spinal cord dorsal horn.[84] Sixth, persistent nociceptive responses in the formalin test are significantly reduced following treatment with the neurokinin antagonists [D-Pro^2, D-Trp^{7,9}] substance P and [D-Pro^4, D-Trp^{7,9,10}, Phe^{11}] substance P[106].

Additional evidence implicates a contribution of excitatory amino acids to central sensitization. First, intrathecal administration of the excitatory amino acids L-glutamate or L-aspartate produces an increase in the excitability of flexor efferents.[128] Second, hyperalgesia in the hind limb contralateral to a thermal injury is mimicked by intrathecal treatment with N-methyl-D-aspartate (NMDA), and reversed by treatment with the NMDA antagonist D-2-amino-5-phosphonovalerate.[25] Third, repetitive C-fiber stimulation produces a wind-up of dorsal horn neuron activity that is mimicked by the intrathecal application of L-glutamate, NMDA, and quisqualate[82] and blocked by the application of the NMDA antagonists D-2-amino-5-phosphonovalerate and MK-801 to the preparation.[35, 39] Fourth, subcutaneous injection of formalin produces an increased release of glutamate and aspartate in spinal cord dorsal horn.[120] Fifth, sustained responses of spinal nociceptive cells to noxious peripheral stimulation with subcutaneous formalin are reduced by selective NMDA antagonists.[61] Sixth, persistent nociceptive responses to formalin-induced tissue injury[29, 106] or hyperalgesia and pain associated with nerve injury in rats[34, 119] are significantly reduced by pretreatment with selective NMDA antagonists. Furthermore, an interaction of neuropeptides and excitatory amino acids is suggested by the finding that intrathecal administration of substance P enhances the release of glutamate and aspartate from spinal cord dorsal horn, and calcitonin gene-related peptide, although not effective on its own, potentiates the effect of substance P.[121]

Cellular Messengers Involved in Central Sensitization

It is apparent that both C-fiber neuropeptides and excitatory amino acids contribute to central sensitization. However, because these transmitters produce effects that last at most seconds to minutes, it is not clear how these substances can produce central changes that last for prolonged (hours to days) periods. It is possible that neuropeptides and excitatory amino acids trigger alterations in membrane excitability through interactions with second messenger systems and protein kinases, which phosphorylate substrate proteins.[107] In recent studies[21, 30] we have begun to assess the contribution of second messenger systems and protein kinases to the development of persistent pain following formalin-induced tissue injury. These studies suggest that increased intracellular calcium is critical to the development of persistent pain associated with central sensitization in the formalin test. Thus, increasing intracellular calcium either with the calcium ionophore A23187 or the calcium channel activator Bay K-8644 significantly increases the persistent nociceptive responses elicited by subcutaneous formalin injection.[30] Conversely, blocking increases in intracellular calcium, with either the calcium chelator quin 2 or the calcium channel antagonist nifedipine, produces a significant reduction in the persistent pain responses to formalin injury.[30]

In addition, evidence suggests that persistent pain after formalin-induced tissue injury is dependent on Ca^{2+}/diacyclglycerol/phospholipid-dependent protein kinase activity.[21] In this study we examined the effects of second messengers and protein kinases on pain related to formalin-induced tissue injury.[21] Formalin pain scores were unaffected by forskolin and H-9, which affect cAMP and cAMP-dependent protein kinase, respectively. Formalin pain scores were also weakly affected by quinacarine, which by inhibiting phospholipase A_2 blocks the conversion of phosphatidylcholine to arachidonic acid, and by W-7, which inhibits Ca^{2+}/calmodulin-dependent protein kinase. By contrast, formalin pain scores were significantly inhibited by neomycin, which by inhibiting phospholipase C (PLC) blocks the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol trisphosphate and diacyclglycerol, and by H-7, which inhibits protein kinase C (PKC). Furthermore, formalin pain scores were significantly enhanced by phorbal 12-myristate 13-acetate and SC-10, which stimulate PKC.[21] As outlined in Figure 5, we hypothesize that following an intense activation of C-fiber afferents,[64] formalin produces a release of glutamate and aspartate from the dorsal horn,[120] which by acting at ionotropic (NMDA) and metabotropic excitatory amino acid receptors, respectively, leads to an influx of Ca^{2+} [96, 99] and the activation of PLC.[124] PLC catalyzes the breakdown of PIP_2 into diacyclglycerol, and thus, leads to the production of PKC, which is activated during high rates of Ca^{2+} influx.[114] By phosphorylating substrate proteins, PKC would produce sustained

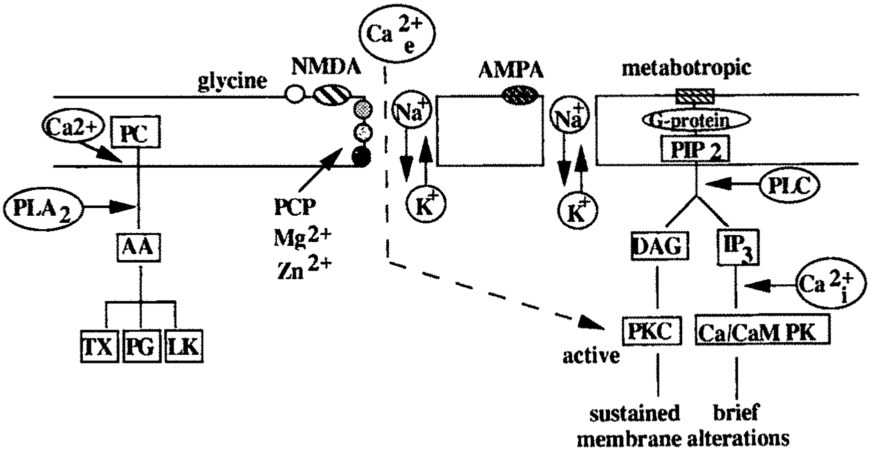


Figure 5. Schematic diagram indicating a possible mechanism by which formalin-induced tissue injury leads to central sensitization of spinal cord dorsal horn neurons. A high level of neural activity induced by formalin injury leads to a release of aspartate and glutamate from dorsal horn neurons. Repetitive activity at the AMPA receptor produces a membrane depolarization that would counter a voltage-dependent blockade of the NMDA receptor by Mg^{2+}. By a further action at NMDA and metabotropic receptors, respectively, excitatory amino acids would produce an influx of Ca^{2+}, and the activation of PLC. PLC catalyzes the hydrolysis of PIP_2, producing IP_3 and DAG, both of which act as intracellular second messengers. In particular, DAG stimulates the production of PKC, which is activated during high rates of Ca^{2+} influx. The activated PKC induces sustained alterations in the cellular membrane affecting membrane permeability for prolonged periods. The production of IP_3 causes the release of calcium from intracellular stores within the reticular formation, and the increased calcium activates calcium/calmodulin-dependent protein kinase (Ca/CaM PK). The production of Ca/CaM PK induces brief membrane alterations that are likely not critical to central sensitization induced by formalin injury. The increased influx of extracellular calcium also activates phospholipase A_2 (PLA_2), which catalyzes the conversion of phosphatidylcholine (PC) to arachidonic acid (AA). AA can undergo a further conversion to thromboxanes (TX), prostaglandins and prostacyclins (PG), or leukotrienes (LT). It is expected that this pathway is not critical for central sensitization following formalin injury. Further investigations are required to determine the contribution of other components of the NMDA-receptor complex (glycine, Zn^{2+}, and others) to plasticity in this model.

membrane alterations, including changes in ion channel conductances,[1, 37] contributing to persistent pain after formalin-induced tissue injury.

Molecular Events Associated with Central Sensitization

In addition to the production of intracellular second messengers, noxious stimulation leads to the expression of proto-oncogenes or third messengers. Hunt et al[69] first demonstrated that the proto-oncogene c-*fos* is expressed in postsynaptic dorsal horn neurons for 24 hours following noxious thermal or chemical (mustard oil applied to skin) stimulation of the skin. The expression of c-*fos* has also been demonstrated in rat spinal dorsal horn in response to noxious pinch of the hind paws,[14] the injection of formalin[79, 112] or carageenan[118] into a hind paw or sodium urate crystals into joints,[102] the induction of polyarthritis with Freund's adjuvant,[102] the production of a neuroma following nerve injury,[19] and the injection of acetic acid into viscera.[102] Noxious stimulation also leads to the expression of additional early immediate genes, including c-*jun*, NGFI-A, NGFI-B, and SRF[65, 133] in spinal cord. Furthermore, following noxious and inflammatory stimuli there is an expression of c-*fos* in the CNS structures involved in pain transmission, including the periaqueductal gray, thalamus, habenula, and somatosensory cortex.[14, 65, 71] Importantly, there is a strong correlation between pain behavior and the number of cells expressing c-*fos*, and morphine pretreatment produces a dose-dependent suppression of c-*fos* expression that corresponds with its analgesic effects.[112, 127]

Because an elevation of intracellular calcium is crucial to the transcriptional activation of c-*fos*,[104] it has been suggested that c-*fos* is induced in spinal cord dorsal horn following Ca^{2+} entry through NMDA receptor-operated calcium channels.[47] Indeed, NMDA receptor activation leads to the expression of c-*fos* in cerebellar granule cells.[125] While its has been demonstrated that noxious stimulation-induced expression of c-*fos* in the spinal dorsal horn is substantially reduced by pretreatment with the NMDA receptor antagonist MK-801,[79] others have found that NMDA antagonists do not affect the distribution of fos labeled neurons in spinal cord.[127, 133] This discrepancy may depend on differences in the nature of the noxious stimulus applied to the periphery (chemical versus thermal stimulation), or specific differences in experimental methods, such as the type of anesthetic agent used. C-*fos* is also expressed in response to phorbol esters and protein kinase C, as well as calcium ionophores when combined with agents which increase cAMP.[113] Thus, it is possible that early immediate genes, such as c-*fos*, are triggered by calcium influx and the stimulation of second messengers and protein kinases following the activation of excitatory amino acid and other receptors. These molecular events may trigger prolonged cellular changes that could account for long-lasting central sensitization and persistent hyperalgesia.

Although there is evidence that noxious stimulation leads to the expression of proto-oncogenes, such as c-*fos*, this does not necessarily mean that these third messengers are involved in central sensitization. However, there is one piece of evidence to suggest that proto-oncogenes indeed may be involved in central sensitization. Recently, Herdegen et al[65] demonstrated that while "low-level" noxious cutaneous stimulation to one hind paw induced c-*fos* in only a few neurons, the same stimulus repeated 1 hour later in the contralateral hind paw induced dense fos labeling in numerous neurons. This suggests that the proto-oncogenes, such as c-*fos*, may be involved in central sensitization. These data are also consistent with the suggestion that molecular events such as new gene expression may be involved in the production of prolonged cellular changes necessary for long-term memory[55] and cellular phenomena that underlie the persistence of chronic pain and hyperalgesia following injury.

CONCLUSION

Tissue injury and acute pain trigger neural and cellular changes that result in local inflammation and peripheral and central sensitization within pain transmission neurons. Peripheral events, including the release or production of toxic substances from tissue or blood, trigger pain and sensitize nociceptors, resulting in increased pain sensitivity or hyperalgesia. Furthermore, the release of neuropeptides, such as substance P, from the peripheral terminals of primary afferent C fibers leads to a spreading of inflammation and hyperalgesia to distant uninjured tissue.

Tissue injury and acute pain also produce a sensitization of CNS neurons, leading to spontaneous pain, referred pain, and hyperalgesia, which may persist for prolonged periods and may outlast the tissue damage that triggered it in the first place. Central sensitization is reflected by wind up, reduced thresholds and the expansion of the receptive fields in dorsal horn neurons, alterations in flexion reflexes, and persistent spontaneous pain, which is maintained in the absence of inputs from the peripheral injury. Central sensitization is influenced by neurochemical (neuropeptides and excitatory amino acids), intracellular second messengers (calcium, diacyclgycerol, protein kinase C), and molecular events (expression of c-*fos*), which trigger changes in ion channel permeability and allow for prolonged alterations in the neurons responses to subsequent stimuli.

It is hoped that through a greater understanding of the responses of both peripheral and CNS structures to tissue injury and acute pain, it may be possible to prevent the tragic conversion of a normal, protective system involved in pain-signaling into a system that triggers pathologic pain of long duration, which we know as chronic pain.

ACKNOWLEDGMENTS

This work was supported by grants from the Medical Research Council of Canada (MT-11045) and Fonds de la Recherche en Santé du Québec (900051).

References

1. Alkon DL, Kubota M, Neary JT, et al: C-kinase activation prolongs Ca^{++}-dependent inactivation of K^+ currents. Biochem Biophys Res Commun 134:1245, 1986
2. Andrews TM, Holton P: The substance P and adenosine triphosphate (ATP) contents of sensory nerves on degeneration. J Physiol 143:45, 1958
3. Angaard E, Jonsson CE: Efflux of prostaglandins in lymph from scalded tissue. Acta Physiol Scand 81:440, 1971
4. Armstrong D, Keele CA, Jepson JB, et al: Development of pain-producing substance in human plasma. Nature 174:791, 1954
5. Bach S, Noreng MF, Tjéllden NU: Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 33:297, 1988
6. Bayliss WM: On the origin from the spinal cord of the vasodilator fibers of the hind limb, and the nature of these fibers. J Physiol 26:173, 1901
7. Beck PW, Handwerker HO: Bradykinin and serotonin effects on various types of cutaneous nerve fibers. Pfleuger's Arch 347:209, 1974
8. Beitel RE, Dubner R: Response of unmyelinated (c) polymodal nociceptors to thermal stimuli applied to monkey's face. J Neurophysiol 39:1160, 1976
9. Bessou P, Perl ER: Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. J Neurophysiol 32:1025, 1969
10. Bilisoly FN, Goodell H, Wolff HG: Vasodilatation, lowered pain threshold, and increased tissue vulnerability. Arch Intern Med 94:759, 1954
11. Blumenkopf B, Lipman JJ: Studies in autotomy: Its pathophysiology and usefulness as a model of chronic pain. Pain 45:203, 1991
12. Broadbent JL: Observations on itching produced by cowhage, and on the part played by histamine as a mediator of the itch sensation. Br J Pharmacol 8:263, 1953
13. Bruce AN: Vasodilator axon reflexes. Q J Exp Physiol 6:339, 1913
14. Bullit E: Induction of c-*fos*-like protein within the lumbar spinal cord and thalalmus of the rat following peripheral stimulation. Brain Res 493:391, 1989
15. Campbell JN, Meyer RA, Raja SN: Hyperalgesia: New insights. Pain Suppl 2:S3, 1984
16. Celander DR, Folkow B: The nature and distribution of afferent fibres provided with the axon reflex arrangement. Acta Physiol Scand 29:359, 1953
17. Chahl LA, Ladd RJ: Local oedema and general excitation of cutaneous sensory receptors produced by electrical stimulation of the saphenous nerve in the rat. Pain 2:25, 1976
18. Chapman LF, Ramos AO, Goodell H, et al: Neurohumoral features of afferent fibers in man. Arch Neurol 4:617, 1961
19. Chi SI, Levine JD, Basbaum AI: Time course of peripheral neuroma-induced expression of Fos protein immunoreactivity in the spinal cord of rats and effects of local anesthetics. Soc Neurosci Abstr 16:566, 1990
20. Chung JM, Kenshalo DR Jr, Gerhart KD, et al: Excitation of primate spinothalamic neurons by cutaneous C-fiber volleys. J Neurophysiol 42:1354, 1979
21. Coderre TJ: Contribution of protein kinase C to persistent pain following subcutaneous formalin injection [abstr 178.18]. Soc Neurosci Abstr 17:438, 1991
22. Coderre TJ, Basbaum AI, Levine JD: Neural control of vascular permeability: Interactions between primary afferents, mast cells and sympathetic efferents. J Neurophysiol 62:48, 1989
23. Coderre TJ, Grimes RW, Melzack R: Autotomy after nerve sections in the rat is influenced by tonic descending inhibition from locus coeruleus. Neurosci Lett 67:82, 1986
24. Coderre TJ, Grimes RW, Melzack R: Deafferentation and chronic pain in animals: An evaluation of evidence suggesting autotomy is related to pain. Pain 26:61, 1986
25. Coderre TJ, Melzack R: Central neural mediators of secondary hyperalgesia following heat injury in rats: Neuropeptides and excitatory amino acids. Neurosci Lett 131:71, 1991
26. Coderre TJ, Melzack R: Cutaneous hyperalgesia: Contribution of the peripheral and

central nervous systems to the increase in pain sensitivity after injury. Brain Res 404:95, 1987

27. Coderre TJ, Melzack R: Increased pain sensitivity following heat injury involves a central mechanism. Behav Brain Res 15:259, 1985
28. Coderre TJ, Melzack R: Procedures which increase acute pain sensitivity also increase autotomy. Exp Neurol 92:713, 1986
29. Coderre TJ, Melzack R: The contribution of excitatory amino acids to central sensitization and persistent nociception after formalin-induced tissue injury. J Neurosci 1992, in press
30. Coderre TJ, Melzack R: The role of NMDA receptor-operated channels in persistent nociception after formalin-induced tissue injury. J Neurosci 1992, in press
31. Coderre TJ, Vaccarino AL, Melzack R: Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. Brain Res 535:155, 1990
32. Cook AJ, Woolf CJ, Wall PD, et al: Dynamic receptive field plasticity in rat spinal dorsal horn following C-primary afferent input. Nature 325:151, 1987
33. Cuello AC, Del Fiacco M, Paxinos G: The central and peripheral ends of the substance P containing sensory neurones in the rat trigeminal system. Brain Res 152:499, 1978
34. Davar G, Maciewicz A: MK-801 blocks thermal hyperalgesia in a rat model of neuropathic pain [abstract 188.12]. Soc Neurosci Abstr 15:472, 1989
35. Davies SN, Lodge D: Evidence for involvement of N-methylaspartate receptors in "wind-up" of class 2 neurones in the dorsal horn of the rat. Brain Res 424:402, 1987
36. Dennis SG, Melzack R: Self mutilation after dorsal rhizotomy in rats: Effects of prior pain and pattern of root lesions. Exp Neurol 65:412, 1979
37. DeReimer SA, Strong JA, Albert KA, et al: Enhancement of calcium current in *Aplysia* neurons by phorbal ester and protein kinase C. Nature 313:313, 1985
38. Devor M, Wall PD: Reorganisation of spinal cord sensory map after peripheral nerve injury. Nature 276:75, 1978
39. Dickenson AH, Sullivan AF: Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep dorsal horn neurones following C-fibre stimulation. Neuropharmacology 26:1235, 1987
40. Dickenson AH, Sullivan AF: Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: Differential response to an opiate administered pre or post formalin. Pain 30:349, 1987
41. DiRosa M, Giroud JP, Willoughby DA: Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. J Pathol 104:15, 1971
42. Dubner R, Sumine R, Wood WI: A peripheral "cold" fiber population responsive to innocuous and noxious thermal stimuli applied to the monkey's face. J Neurophysiol 38:1373, 1975
43. Dubuisson D, Dennis SG: The formalin test: A quantitative study of the analgesic effects of morphine, meperidine, and brain stem stimulation in rats and cats. Pain 4:161, 1977
44. Echlin F, Propper N: 'Sensitization' by injury of the cutaneous nerve endings in the frog. J Physiol 88:388, 1937
45. Ferreira SH: Prostaglandins, aspirin-like drugs and analgesia. Nature New Biol 240:200, 1972
46. Fewtrell CMS, Fooreman JC, Jordan CC, et al: The effects of substance P on histamine and 5-hydroxytryptamine release in the rat. J Physiol 330:393, 1982
47. Fitzgerald M: C-*fos* and the changing face of pain. Trends Neurosci 13:439, 1990
48. Fitzgerald M: The spread of sensitization of polymodal nociceptors in the rabbit from nearby injury and by antidromic nerve stimulation. J Physiol 297:207, 1979
49. Fitzgerald M, Lynn B: The sensitization of high threshold mechanoreceptors with myelinated axcons by repeated heating. J Physiol 365:549, 1977
50. Fjällbrant N, Iggo A: The effect of histamine, 5-hydroxytryptamine and acetylcholine on cutaneous afferent fibers. J Physiol 156:578, 1961
51. Fock S, Mense S: Excitatory effects of 5-hydroxytryptamine, histamine and potassium ions on muscular group IV afferent units: A comparison with bradykinin. Brain Res 105:459, 1976

52. Foreman JC, Jordan CC: Comparison of the activities of some peptides in human skin and as histamine releasing agents. Br J Pharmacol 73:207, 1981
53. Foreman JC, Jordan CC, Oehme P, et al: Structure-activity relationships for some substance P-related peptides that cause wheal and flare reactions in human skin. J Physiol 335:449, 1983
54. Gasser H: Unmedulated fibres originating in dorsal root ganglia. J Gen Physiol 33:651, 1950
55. Goelet P, Castellucci VF, Schacher S, et al: The long and the short of long-term memory—A molecular framework. Nature 322:419, 1986
56. Goltz F: Uber gefasserweiternde nerven. Pflueger's Arch Gen Physiol 9:185, 1874
57. Gonzales R, Goldyne ME, Taiwo YO, et al: Production of hyperalgesic prostaglandins by sympathetic postganglionic neurons. J Neurochem 53:1595, 1989
58. González-Darder JM, Barberá J, Abellán MJ: Effects of prior anesthesia on autotomy following sciatic transections in rats. Pain 24:87, 1986
59. Greaves M, Shuster S: Responses of skin blood vessels to bradykinin, histamine and 5-hydroxytryptamine. J Physiol 193:255, 1967
60. Hägermark O, Hökfelt T, Pernow B: Flare and itch induced by substance P in human skin. J Invest Dermatol 71:233, 1978
61. Haley JE, Sullivan AF, Dickenson AH: Evidence for spinal N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. Brain Res 518:218, 1990
62. Handwerker HO: Influences of algogenic substances and prostaglandins on the discharges of unmyelinated cutaneous nerve fibers identified as nociceptors. *In* Bonica JJ, Albe-Fessard D (eds): Advances in Pain Research and Therapy, vol 1. New York, Raven Press, 1976, p 41
63. Hardy JD, Wolff HG, Goodell H: Experimental evidence on the nature of cutaneous hyperalgesia. J Clin Invest 29:115, 1950
64. Heapy CG, Jamieson A, Russell NJW: Afferent C-fibre and A-delta activity in models of inflammation. Br J Pharmacol 90:164P, 1987
65. Herdegen T, Leah JD, Walter T, et al: Noxious stimulation induces molecular genetic events in neurons of the central nervous system: Expression of immediate-early gene encoded protein products. *In* Bond MR, Charlton JE, Woolf CJ (eds): Pain Research and Clinical Management, vol 4. Proceedings of the VIth World Congress on Pain. Amsterdam, Elsevier, 1991, p 325
66. Hoheisel U, Mense S: Long-term changes in discharge behaviour of cat dorsal horn neurones following noxious stimulation of deep tissues. Pain 36:231, 1989
67. Hökfelt T, Johannson O, Kellerth JO, et al: Immunohistochemical distribution of substance P. *In* von Euler US, Pernow B (eds): Substance P: Nobel Symposium 37. New York, Raven Press, 1977, p 117
68. Holmdahl G, Leander RHS, Rossell S, et al: A substance P antagonist [D-Pro2, D-Trp7,9]SP, inhibits inflammatory responses in the rabbit eye. Science 214:1029, 1981
69. Hunt SP, Pini A, Evan G: Induction of c-*fos*-like protein in spinal cord neurons following sensory stimulation. Nature 328:632, 1987
70. Hylden JLK, Nahin RL, Traub RJ, et al: Expansion of receptive fields of spinal lamina I projection neurones in rats with unilateral adjuvant-induced inflammation: The contribution of dorsal horn mechanisms. Pain 37:229, 1989
71. Iadorola MJ, Sanders SR, Draisci G: Neuropeptide and c-*fos* gene expression in periaqueductal grey (PAG) during peripheral inflammation. Pain Suppl 5:S270, 1990
72. Johnson AR, Erdos EG: Release of histamine from mast cells by vasoactive peptides. Proc Soc Exp Biol Med 142:1252, 1973
73. Jonsson C-E, Shimizu Y, Fredholm BB, et al: Efflux of cyclic AMP, prostaglandin E_2 and F_2 and thromboxane B_2 in leg lymph of rabbits after scalding injury. Acta Physiol Scand 107:377, 1979
74. Juan H, Lembeck F: Action of peptides and other algesic agents on paravascular pain receptors of the isolated perfused rabbit ear. Naunyn Schmiedebergs Arch Pharmacol 283:151, 1974
75. Juhlin S, Michaelson G: Cutaneous vascular reactions to prostaglandins in healthy subjects and in patients with urticaria and atopic dermatitis. Acta Derm Venereol (Stockh) 49:251, 1969

76. Karim SMM: Action of prostaglandins in the pregnant woman. Ann NY Acad Sci 180:483, 1971
77. Katz J, Vaccarino AL, Coderre TJ, et al: Injury prior to neurectomy alters the pattern of autotomy in rats: Behavioural evidence of central neuroplasticity. Anesthesiology 75:876, 1991
78. Keele CA, Armstrong D: Substances producing pain and itch. London, Edward Arnold, 1964
79. Kehl LJ, Gogas KR, Lichtblau L, et al: The NMDA antagonist MK-801 reduces noxious stimulus-evoked Fos expression in the spinal dorsal horn. *In* Bond MR, Charlton JE, Woolf CJ (eds): Pain Research and Clinical Management, vol 4. Proceedings of the VIth World Congress on Pain. Amsterdam, Elsevier, 1991, p 307
80. Kenins P: Identification of the unmyelinated sensory nerves which evoke plasma extravasation in response to antidromic stimulation. Neurosci Lett 25:137, 1981
81. Kenshalo DR Jr, Leonard RB, Chung JM, et al: Responses of primate spinothalamic neurons to graded and to repeated noxious heat stimuli. J Neurophysiol 42:1370, 1979
82. King AE, Thompson SWN, Urban L, et al: An intracellular analysis of amino acid induced excitations of deep dorsal horn neurones in the rat spinal cord slice. Neurosci Lett 89:286, 1988
83. Kumazawa T, Perl ER: Primate cutaneous sensory units with unmyelinated (c) afferent fibers. J Neurophysiol 6:1325, 1977
84. Kuraishi Y, Hirota N, Sato Y, et al: Stimulus specificity of peripherally evoked substance P release from the rabbit dorsal horn in situ. Neurosci Lett 30:241, 1989
85. LaMotte RH, Thalhammer JG, Robinson CJ: Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: A comparison of neural events in monkey with sensory judgment in human. J Neurosci 50:1, 1983
86. Langley JN, Anderson HK: On reflex action from sympathetic ganglia. J Physiol 16:410, 1894
87. Lembeck F: Zur frage der zentralen übertragung afferenter impulse. Mitteilung. Das vorkommen und die bedentung der substanz P in den dorsalen wurzeln des rückenmarks. Naunyn Schmiedeberg's Arch Exp Path Pharmacol 219:197, 1953
88. Lembeck F, Folkers K, Donnerer J: Analgesic effect of intraspinally injected substance P antagonists. Biochem Biophys Res Commun 103:1318, 1981
89. Lembeck F, Gamse R: Substance P in peripheral sensory processes. *In* Porter R, O'Connor M (eds): Substance P in the Nervous System. Ciba Foundation Symposium 91. London, Pitman, 1982, p 35
90. Lembeck F, Holtzer P: Substance P as neurogenic mediator of antidromic vasodilatation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch Pharmacol 310:175, 1979
91. Levine JD, Lau W, Kwiat G, et al: Leukotriene B_4 produces hyperalgesia that is dependent on polymorphonuclear leukocytes. Science 225:743, 1984
92. Lewis T: Pain. New York, MacMillan, 1942
93. Lewis T: The nocifensor system of nerves and its reactions. Br Med J 194:431, 491, 1937
94. Lewis T, Marvin HM: Observations relating to vasodilatation arising from antidromic impulses to herpes zoster and trophic effects. Heart 14:27, 1927
95. Lynn B, Carpenter SE: Primary afferent units from the hairy skin of the rat hindlimb. Brain Res 238:29, 1982
96. MacDermott AB, Mayer ML, Westbrook GL, et al: NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. Nature 321:519, 1986
97. Markus H, Pomeranz B, Krushelnycky D: Spread of saphenous projection map in spinal cord and hypersensitivity of the foot after chronic sciatic denervation in adult cat. Brain Res 296:27, 1984
98. Martin HA, Basbaum AI, Goetzl EJ, et al: Leukotriene B_4 decreases the mechanical and thermal thresholds of C-fiber nociceptors in the hairy skin of the rat. J Neurophysiol 60:438, 1988
99. Mayer ML, Westbrook GL, Guthrie PB: Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. Nature 309:261, 1986
100. McMahon SB, Wall PD: Receptive fields of rat lamina 1 projection cells move to incorporate a nearby region of injury. Pain 19:235, 1984

101. Mendell LM: Physiological properties of unmyelinated fiber projections to the spinal cord. Exp Neurol 16:316, 1966
102. Menétrey D, Gannon A, Levine JD, et al: Expression of c-*fos* protein in interneurons and projection neurons of the rat spinal cord in response to noxious somatic, articular, and visceral stimulation. J Comp Neurol 285:177, 1989
103. Meyer RA, Campbell JN: Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. Science 213:1527, 1981
104. Morgan JI, Curran T: Role of ion flux in the control of c-*fos* expression. Nature 322:552, 1986
105. Müller LR: Studien über der dermographismus und dessen diagnostische bedeutung. Dtsch Z Nervenheilk 47:413, 1913
106. Murray CW, Cowan A, Larson AA: Neurokinin and NMDA antagonists (but not a kainic acid antagonist) are antinociceptive in the mouse formalin model. Pain 44:179, 1991
107. Nestler EJ, Greengard P: Protein phosphorylation in the brain. Nature 305:583, 1983
108. Oehme P, Bergmann J, Bienert M, et al: Biological action of substance P—its differentiation by affinity and intrinsic efficacy. *In* von Euler US, Pernow B (eds): Substance P. New York, Raven Press, 1977, p 327
109. Olgart L, Gazelius B, Brodin E, et al: Release of substance P-like immunoreactivity from dental pulp. Acta Physiol Scand 101:510, 1977
110. Perl ER: Sensitization of nociceptors and its relation to sensation. *In* Bonica JJ, Albe-Fessard D (eds): Advances in Pain Research and Therapy, vol 1. New York, Raven Press, 1976, p 17
111. Perl ER, Kumuzawa T, Lynn B, et al: Sensitization of high threshold receptors with unmyelinated (C) afferent fibres. *In* Iggo A, Ilynsky I (eds): Somatosensory and Visceral Receptor Mechanisms. Prog Brain Res 43:263, 1974
112. Presley RW, Menétrey D, Levine JD et al: Systemic morphine suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in the rat spinal cord. J Neurosci 10:323, 1990
113. Ran W, Dean M, Levine RA, et al: Induction of c-*fos* and c-*myc* mRNA by epidermal growth factor or calcium ionophore is cAMP dependent. Proc Natl Acad Sci USA 83:8216, 1986
114. Rasmussen H: The calcium messenger system. N Engl J Med 314:1094, 1164, 1986
115. Riley JF, West GB: The presence of histamine in tissue mast cells. J Physiol 281:33, 1953
116. Rocha E, Silva M, Rosenthal SR: Release of pharmacologically active substances from the rat skin in vivo following thermal injury. J Pharmacol Exp Ther 132:110, 1961
117. Rossell S, Olgart L, Gazelius B, et al: Inhibition of antidromic and substance P-induced vasodilatation by a substance P antagonist. Acta Physiol Scand 111:381, 1981
118. Ruda MA, Kowalski K, Traub RJ, et al: Colocalization of opioid peptide and Fos protein in a rat model of peripheral inflammation and hyperalgesia. Pain Suppl 5:S102, 1990
119. Seltzer Z, Cohn S, Ginzburg R, et al: Modulation of neuropathic pain behavior in rats by spinal disinhibition and NMDA receptor blockade of injury discharge. Pain 45:69, 1991
120. Skilling SR, Smullin DH, Larson AA: Extracellular amino acid concentrations in the dorsal spinal cord of freely moving rats following veratridine and nociceptive stimulation. J Neurochem 51:127, 1988
121. Smullin DH, Skilling SR, Larson AA: Interaction between substance P, calcitonin gene related peptide, taurine and excitatory amino acids in the spinal cord. Pain 42:93, 1990
122. Spiess G: Die bedentung der anasthesie in der entzundungs-therapie. Münch Med Wochensch 53:345, 1906
123. Sturge WA: The phenomena of angina pectoris and their bearing upon the theory of counter-irritation. Brain 5:492, 1883
124. Sugiyama H, Ito I, Hirono C: A new type of glutamate receptor linked to inositol phospholipid metabolism. Nature 325:551, 1987

125. Szekely AM, Barbaccia ML, Alho H, et al: In primary cultures of cerebellar granule cells the activation of N-methyl-D-aspartate-sensitive glutamate receptors induces c-*fos* mRNA expression. Mol Pharmacol 35:401, 1989
126. Thalhammer JG, LaMotte RH: Spatial properties of nociceptor sensitization following heat injury of the skin. Brain Res 231:257, 1982
127. Tolle TR, Castro-Lopes JM, Evan G, et al: C-*fos* induction in the spinal cord following noxious stimulation: Prevention by opiates but not by NMDA antagonists. *In* Bond MR, Charlton JE, Woolf CJ (eds): Pain Research and Clinical Management, vol 4. Proceedings of the VIth World Congress on Pain. Amsterdam, Elsevier, 1991, p 299
128. Torebjörk HE, LaMotte RH, Robinson CJ: Peripheral neural correlation of magnitude of cutaneous pain and hyperalgesia: Simultaneous recordings in humans of sensory judgments of pain and evoked response in nociceptors with C-fibres. J Neurophysiol 51:325, 1984
129. Urban L, Randic M: Slow excitatory transmission in rat dorsal horn: Possible mediation by peptides. Brain Res 290:336, 1984
130. Wall PD, Woolf CJ: Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol 356:443, 1984
131. White DM, Basbaum AI, Goetzl EJ, et al: The 15-lipoxygenase product, 8R, 15S-diHETE, stereospecifically sensitizes C-fiber mechanoheat nociceptors in hairy skin of rat. J Neurophysiol 63:966, 1990
132. Wiesenfeld-Hallin Z: Somatostatin and calcitonin gene related peptide synergistically modulate spinal sensory and reflex mechanisms in the rat: Behavioral and reflex electrophysiological studies. Neurosci Lett 67:319, 1986
133. Wisden W, Errington ML, Williams S, et al: Differential expression of immediate early genes in the hippocampus and spinal cord. Neuron 4:603, 1990
134. Woolf CJ: Evidence for a central component of post-injury pain hypersensitivity. Nature 308:686, 1983
135. Woolf CJ: Long term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. Pain 18:325, 1984
136. Woolf CJ, McMahon SB: Injury-induced plasticity of the flexor reflex in chronic decerebrate rats. Neuroscience 16:395, 1985
137. Woolf CJ, Wall PD: Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexion reflex in the rat. J Neurosci 6:1433, 1986
138. Woolf CJ, Wiesenfeld-Hallin Z: Substance P and calcitonin gene-related peptide synergistically modulate the gain of the nociceptive flexor withdrawal reflex in the rat. Neurosci Lett 66:226, 1986

Address reprint requests to

Terence J. Coderre, PhD
Pain Mechanisms Laboratory
Clinic Research Institute of Montreal
110 Pine Avenue West
Montreal, Quebec
Canada H2W 1R7

NEW TECHNIQUES OF OPIOID ADMINISTRATION FOR THE CONTROL OF ACUTE PAIN

Alan N. Sandler, MB ChB, FRCPC

The use of opioids to control acute pain has roots in ancient history,[27] and opioids are still the primary analgesic agents chosen for severe pain. Improvements in pain relief in recent times have not stemmed from major changes in these agents but in the administration techniques that have been developed and used with great success. In the forefront of the newer technologies are spinal opioid administration and patient-controlled analgesia. These topics are discussed elsewhere in this volume. However, several other novel administration techniques are under intensive investigation or in current use.[45] These include the oral mucosal opioids (buccal, sublingual, and oral lozenges) and intranasal, rectal, and transdermal opioids. Oral lozenges (oral transmucosal fentanyl[36]) and nasal preparations (sufentanil spray or drops[49]) have been studied as preanesthetic premedication and are currently being evaluated for the relief of acute pain. Oral transmucosal opioids are available for commercial use for postoperative pain in some parts of the world, and specially designed rectal opioid preparations are at the point of clinical investigation.[24] Transdermal fentanyl is currently under intensive study and is available for chronic pain related to neoplastic disease in the United States.

ORAL MUCOSAL ADMINISTRATION

Oral mucosal administration has used the buccal mucosal route (morphine[1]) or the sublingual route (phenazocine,[9] buprenorphine[10–12])

From the Department of Anaesthesia, University of Toronto; and Department of Anaesthesia, Toronto General Division, The Toronto Hospital, Toronto, Ontario, Canada

to administer opioids for postoperative pain control. Buccal and sublingual tissues (approximately 200 cm^2 total area) are rich in blood vessels and lymphatics through which opioids are absorbed. Venous drainage is directly into the systemic circulation and thus avoids gastrointestinal degradation and hepatic first-pass metabolism. Transfer of opioids across the buccal mucosa is related to the lipophilicity of the drug. Patient acceptance factors include lack of bad taste and corrosive action. Buccal morphine was administered to postoperative orthopedic patients as a tablet placed between the upper lip and the gum above the incisor teeth and slowly dissolved within 6 hours. A similar degree of analgesia and onset time was found when compared with intramuscular morphine in a double-blind fashion. An advantage was a slower decline in plasma morphine concentrations with the buccal route, with a resulting increase in bioavailability of morphine after buccal administration.[1] However, other volunteer studies have not demonstrated this increased bioavailability of morphine after buccal administration.[20] Sublingual opioids were used more than 20 years ago by Brown,[9] who found sublingual phenazocine to be as effective as intramuscular phenazocine for postoperative analgesia. Buprenorphine, a partial agonist/antagonist seems particularly suitable for sublingual use. It has good lipophilic properties (five times morphine) and presents high bioavailability (55% of the dose).[11] It is a potent analgesic with a long duration of action (0.4 mg given sublingually lasts approximately 8 hours). However, the terminal elimination half-life is much shorter (5 hours), and the prolonged duration of action has been explained by the high affinity, slow association, and even slower dissociation from opioid receptors found for buprenorphine.[5, 23] Because of the high hepatic clearance of buprenorphine, any drug that is accidently swallowed is effectively metabolized and cleared by the liver and does not participate in the drug effects. Sublingual absorption of buprenorphine is slow, with peak plasma concentrations occurring 90 to 360 minutes after administration[11] (Fig. 1). Mandatory sublingual buprenorphine, 0.4 mg, administered every 6 or 8 hours postoperatively after abdominal surgery[17] or total hip replacement,[12] respectively, produced good analgesia as the sole method of pain control. Double-blind comparisons with intramuscular morphine[19] and papaveretum[21] demonstrated a slow onset and prolonged duration of action of buprenorphine. There was no difference in the analgesic quality or the incidence of side effects between buprenorphine and the systemically applied opioids in these studies.

Other clinical trials have shown equivalent analgesia postoperatively when compared with comparable doses of intramuscular morphine,[16] meperidine,[15] or buprenorphine.[15, 44] Sublingual buprenorphine is especially suitable for children,[32] who are often unwilling to accept intramuscular injections of opioids. Due to the slow onset of analgesia with sublingual buprenorphine, a loading dose is usually given intravenously toward the end of surgery or in the postanesthetic care unit (PACU).

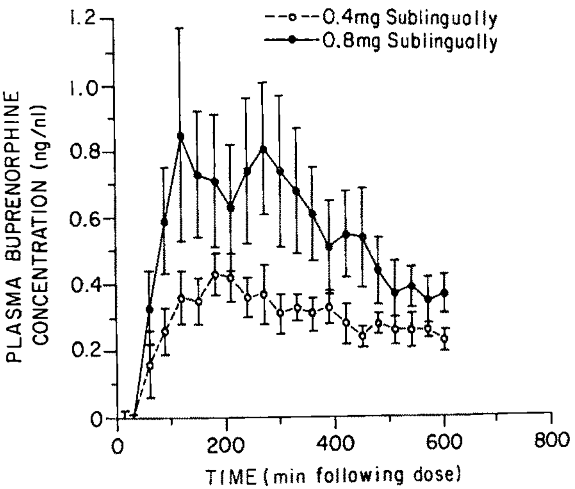


Figure 1. Mean buprenorphine plasma concentrations (ng/mL ± SE) following two doses of sublingual buprenorphine. (*From* Bullingham R, Mcquay H, Porter E, et al: Sublingual buprenorphine used postoperatively: Ten-hour plasma drug concentration analysis. Br J Clin Pharmacol 13:665, 1982; with permission.)

RECTAL ADMINISTRATION

The rectal administration of opioids for acute analgesia has not received a great deal of prominence primarily from cultural or social objections rather than pharmacologic or pharmacokinetic defects.[25] The rectal mucosa, the site of primary absorption of any analgesic drug, has a surface area of 200 to 400 cm^2, approximately 500 to 1000 times smaller than the small intestine. Opioids are absorbed through the mucosa into the submucosal venous plexus, which drains into the superior, middle, and inferior rectal veins. The superior vein drains into the portal system and then into the liver, whereas the middle and inferior veins drain into the systemic circulation via the internal iliac veins and inferior vena cava. The individual variability of the watershed between portal and systemic circulations makes it difficult to predict how much of a drug placed in the rectum will be absorbed into either the portal or systemic circulation. The main advantage of the rectal route is that it is independent of intestinal motility, gastric emptying, and the presence of nausea and vomiting. Morphine is the most widely used opioid given by suppository and has been studied almost exclusively in association with the relief of chronic pain of neoplastic origin.[8, 46] The vehicles for the suppositories have been either fatty substances or tablets in a gelatine capsule, neither of which have provided satisfactory, prolonged administration. Studies assessing the absorption of morphine from solution or in a starch hydrogel paste have shown a wide range of bioavailability with a mean rectal/parenteral ratio of about 30%, which indicates a similar or better absorption rectally than orally.[26, 50] Hanning et al[24] have developed a morphine hydrogel suppository to provide analgesia in acute postoperative conditions. Hydrogels are inert, hydrophilic polymer gels that can be impregnated with water-soluble drugs like morphine. The drug is held within the polymer matrix in the dry state and released on rehydration in a predictable and reproducible manner. By shaping the morphine hydrogel suppository into a cylinder and arranging the concentration of morphine to be greatest on the inner and outer surfaces of the suppository, Hanning et al[24] were able to achieve a plasma pharmacokinetic profile in four patients, suggesting administration of an initial bolus followed by an infusion (Fig. 2). In addition, Hanning et al[24] performed several open pilot studies using two halves of morphine hydrogel suppository joined together, which have produced promising results in small groups of patients for postoperative analgesia.

TRANSDERMAL ADMINISTRATION

The transdermal route is the most recent technique of opioid administration to be developed and holds significant potential for acute pain control. It will be reviewed in some detail here. The interest in this route is related primarily to the advances in the use of prolonged action medication,[35] which have resulted in the development of the transdermal therapeutic system (TTS). TTS has been successful in providing effective, stable serum levels in the chronic use of glyceryl trinitrate for the treatment of angina,[6] hyoscine for motion sickness,[47] clonidine for hypertension,[34] and estrogen replacement therapy.[31] The advantages[35] of an uncomplicated prolonged action delivery system

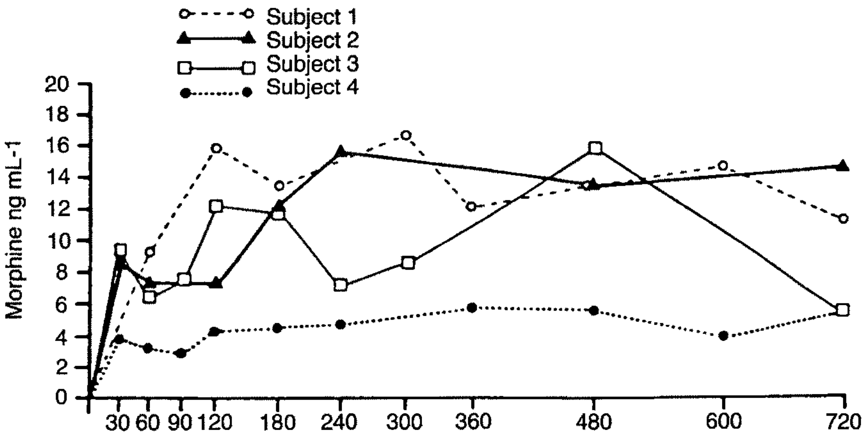


Figure 2. Plasma morphine concentrations after the administration of a morphine hydrogel suppository. (*From* Hanning CD, Vickers AP, Smith G, et al: The morphine hydrogel suppository: A new sustained release rectal preparation. Br J Anaesth 61:221, 1988; with permission.)

providing stable serum levels has prompted investigation into the use of opioids (primarily the lipid-soluble synthetic opioids fentanyl and sufentanil) when administered transdermally for postoperative analgesia. Fentanyl in particular has the advantage of few cardiovascular and sedation-related side effects, and these features coupled with its lipid-soluble properties, allowing percutaneous absorption, make it an attractive candidate for a TTS patch system. The major obstacle to drug absorption is the stratum corneum where diffusion occurs primarily via the intercellular lipid medium.[28] Advantages of TTS-fentanyl include decreased gastrointestinal degradation and first-pass hepatic metabolism, stable plasma concentrations, improved patient compliance through extreme ease of administration, multiday dosage, and decreased risk for any infective process due to lack of needle usage.[33] The major disadvantage of TTS-fentanyl is the inability of the system to respond rapidly to increasing or decreasing analgesic requirements or to the approximately fivefold degree of variability in analgesic requirements between patients. In addition, the potential for abuse with this system may be great. There are four systems that have been developed that provide effective transdermal drug delivery.[45] The TTS-fentanyl patch uses the membrane permeation model (Fig. 3). In this system a drug reservoir is formed from a shallow compartment molded from a drug-impermeable laminate, and the open surface of the compartment is covered by a microporous rate-controlling membrane. The outer surface of this membrane is coated by an adhesive polymer that is in contact with the skin. Large amounts of fentanyl (up to 10 mg) are present in the reservoir in a gel matrix to provide a driving force for diffusion. Increased systemic requirements are accommodated by increasing the size of the TTS-fentanyl patch (25, 50, 75, 100 cm^2). These different patch sizes provide sustained fentanyl infusion rates of approximately 25, 50, 75, and 100 μ/h over periods of up to 72 hours. A substantial amount of fentanyl remains within the system on removal of the patch, which increases the abuse potential of the TTS-fentanyl system. In one study using TTS-fentanyl 100 patches 1.07 ± 0.43 mg of fentanyl remained in the patches after 24 hours of use.[48] An important

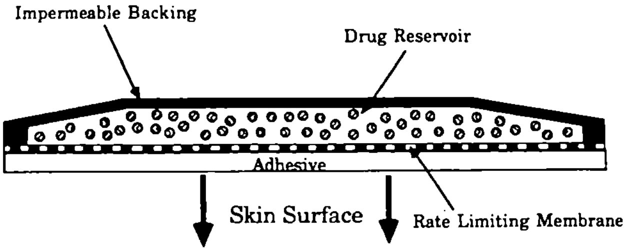


Figure 3. Schematic of membrane permeation transdermal delivery system. (*From* Tarver SD, Stanley TH: Alternative routes of drug administration and new drug delivery systems. *In* Stoelting RK, Barash P, Gallagher TJ (eds): Advances in Anesthesia, vol 7. Chicago, Year Book, 1990, p 337; with permission.)

feature of the TTS-fentanyl patch is that the skin layers, especially the dermis, act as a secondary reservoir that requires filling before sustained systemic absorption occurs. Continued absorption occurs from the skin reservoir after the patch is removed. This characteristic has a marked effect on the pharmacokinetics of the system.

Pharmacokinetics

The TTS-fentanyl system is based on the concept that there is a relationship between plasma-fentanyl concentration and analgesia. The literature relating to the pharmacokinetic characteristics of the system have been well summarized in several recent reviews.[13, 28, 33] In general, once the TTS-fentanyl patch is applied, the plasma-fentanyl concentration increases over 12 to 18 hours until a plateau develops. The plateau plasma-fentanyl concentration remains fairly constant until the patch is removed at which time the plasma concentration decreases slowly, with an apparent half-life of 15 to 21 hours. The application of the TTS-fentanyl 50, TTS-fentanyl 75, and TTS-fentanyl 100 patches produce average plasma concentrations of 1.0, 1.5, and 2.0 ng/mL. However, these concentrations may vary up to 200% of the target levels for individual patients. Plasma concentrations such as these can provide adequate analgesia for a variety of postoperative situations, with the higher concentrations necessary for more major surgery (e.g., postthoracotomy).[28] Several authors have measured pharmacokinetic parameters over a 24-hour period for different sized TTS-fentanyl systems. Duthie et al[18] used a TTS-fentanyl 100 patch and measured peak plasma concentrations between 1.5 and 2.0 ng/mL. Holley and Van Steennis[29] also used a TTS-fentanyl 100 patch and found peak serum fentanyl concentrations of about 2.4 ng/mL at 24 hours. Varvel et al[48] have performed a detailed pharmacokinetic study in eight patients 24 hours after major surgery. Using an intravenous fentanyl infusion at induction they first determined individual fentanyl pharmacokinetics for each subject and then placed TTS-fentanyl 100 patches on the patients 24 hours later for a 24-hour period. Relatively constant serum fentanyl concentrations were seen from 14 to 24 hours (1.8 ± 0.8 ng/mL) although peak concentrations ranged from 1 to 3.8 ng/mL. This study was able to estimate the mean bioavailability (0.92 ± 0.33) of fentanyl by calculating the total fentanyl absorbed and measuring the total fentanyl delivered (residual fentanyl in the patch). The high bioavailability indicated negligible cutaneous metabolism and no significant first-pass drug loss. Gourlay et al[22] assessed a mixture of TTS-fentanyl patches (TTS-fentanyl 50, 75, 100 systems) although 8 of the 13 patients used the TTS-fentanyl 75 patch. In this study significant discrepancies were found in the actual delivery rate of fentanyl for patches with the same nominal delivery rate. The range of actual delivery rates was 48 to 213 μg/h, with a mean of 95 ± 38 μg/h. In another 24-hour patch application study, Caplan et al,[13] using a TTS-fentanyl 50 patch, recorded peak serum fentanyl levels of 1.04 ± 0.43 ng/mL at 24 hours, which decreased to 0.75 ± 0.47 ng/mL 12 hours after patch removal. Longer TTS-fentanyl patch application periods have been studied by Larijani et al.[30] A TTS-fentanyl 75 patch was applied to 10 patients and left in place for 72 hours. The mean concentration was 1.5 ± 0.5 ng/mL, which remained stable for the 72-hour period. The decrease in fentanyl concentration after patch removal had a half-life of 19.6 ± 5.2 hours.

Analgesic Effects

Analgesic effectiveness of TTS-fentanyl patches for acute pain has been exclusively measured in postoperative pain studies. Pain control has been quantified by visual analogue scoring (VAS) systems and by parenteral opioid requirements postoperatively.

In general the clinical studies fall into either an open-label design[2, 3, 4, 22, 29] or formal double-blind, randomized, placebo-controlled clinical trials of TTS-fentanyl versus standard postoperative analgesic regimens[7, 13, 33, 38, 39, 41, 42] (Table 1).

Holley and van Steennis,[29] in an open-label study, used a TTS-fentanyl 100 patch applied 2 hours preoperatively to eight patients (seven thoracotomy, one lumbar fusion). Intraoperatively, 300 μg of fentanyl was given. There were no differences in pain scores compared with patients receiving intravenous infusions of fentanyl although no details were reported. The mean morphine requirement over the 24-hour study was 14.6 ± 6 mg, similar to that in patients who received a fentanyl infusion of 100 μ/h. Sixty percent of the postoperative morphine supplementation was required in the PACU, and this is a recurring observation in many of these studies.[28] Respiratory depression or side effects were not reported.

In 13 patients undergoing abdominal surgery Gourlay et al[22] applied

Table 1. TRANSDERMAL THERAPEUTIC SYSTEM WITH DEMOGRAPHIC DATA OF COMPARATIVE STUDIES

Study	No.	Surgery	Anesthesia	TTS-Fentanyl (μg/h)	APPL/DURN (h/h)	Intraoperative Opioid Dose
Plezia (1988)	43	Orthopedic	General	TTSF-75	2/36	200 μg F
v. Bormann (1988)	40	Hip replacement	Epidural	TTSF-75	0.5/24	0
Caplan (1989)	42	Shoulder repair	Interscalene block	TTSF-75	0/24	100 μg F
Rowbotham (1989)	30	Upper abdominal	General	TTSF-100	2/24	200 μg F
McLeskey (1990)	54	Lower abdominal	General	TTSF-50	2/24	100 μg F
Sandler (1991)	20	Lower abdominal	General	TTSF-50 TTSF-75	2/72	5 μg/kg S

Abbreviations: TTSF = TTS-fentanyl patch; APPL = time of TTS-fentanyl application preoperatively; DURN = duration of TTS-fentanyl use; F = fentanyl; S = sufentanil. *From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.

a variety of TTS-fentanyl patches just before surgery (most were TTS-fentanyl 75 patches) and then changed them 24 hours postoperatively. The second patches were removed after 24 hours. One hundred to 200 μg of fentanyl were given intraoperatively. Pain scores were not formally reported, but all patients required supplementary meperidine postoperatively, particularly in the first 12 hours. Eleven patients were nauseated and, most importantly, three patients demonstrated respiratory depression as bradypneic episodes. Bell et al,[2-4] in another open-label study, assessed the TTS-fentanyl 75 patch in two small groups of patients. One group had the patch changed every 24 hours for 3 days, whereas the other group had the same patch applied for 72 hours. Patches were applied 2 hours before surgery, and all patients were given 300 μg of fentanyl intraoperatively. Pain scores were highest during the first 24 hours postoperatively for both groups as were supplemental morphine requirements. On the basis of respiratory rate there was no evidence of respiratory depression. The incidence of nausea and vomiting was much higher (up to 36%) in the group who had the TTS-fentanyl patches replaced every 24 hours.

In addition to these open-label studies there have been several well-designed clinical trials evaluating the TTS-fentanyl patch. These studies are summarized in Tables 1 to 4.

Plezia et al,[38] using a TTS-fentanyl 75 patch, were unable to demonstrate a significant difference in pain scores between the active and placebo groups in their study, although Caplan et al,[13] Rowbotham et al,[39] and McLeskey[33] found significant between-group differences in pain scores in their studies, the TTS-fentanyl groups having lower pain scores than the placebo group (Table 2). Similarly, although almost all patients required supplemental opioid analgesics, Caplan et al,[13] Rowbotham et al,[39] and McLeskey[33] all found significantly lower analgesic requirements in the TTS-fentanyl patients, whereas the other studies[7, 38, 41, 42] found decreased (nonsignificant) analgesic requirements (Table 3).

Side effects were variable in both types of studies. Bell and Goldberg[3] reported an incidence of nausea and vomiting of approximately 30% if new patches were applied each day, whereas Gourlay et al[22] found nausea occurring in 85% of their patients. Plezia et al[38] described an approximately 30% incidence of nausea and vomiting in both the TTS-fentanyl and placebo groups in their study. Caplan et

Table 2. TRANSDERMAL THERAPEUTIC SYSTEM WITH PAIN CONTROL IN COMPARATIVE STUDIES

Study	Postoperative Pain Control
Plezia (1988)	No between-GP differences
Sandler (1991)	No between-GP differences
v. Bormann (1988)	TTSF GP–decreased pain
Caplan (1989)	TTSF GP–significantly less pain
Rowbotham (1989)	TTSF GP–significantly less pain
McLeskey (1990)	TTSF GP–significantly less pain

Abbreviations: TTSF = fentanyl patch; GP = patient group. *From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.

Table 3. TRANSDERMAL THERAPEUTIC SYSTEM WITH POSTOPERATIVE OPIOID REQUIREMENTS IN COMPARATIVE STUDIES

Study	Postoperative Opioid Required
Plezia (1988)	TTSF GP decreased morphine use
v. Bormann (1988)	TTSF GP decreased meperidine use
Sandler (1991)	TTSF GP decreased morphine use
Caplan (1989)	TTSF GP significantly decreased morphine use
Rowbotham (1988)	TTSF GP significantly decreased morphine use
McLeskey (1990)	TTSF GP significantly decreased morphine use

Abbreviations: TTSF = TTS-fentanyl patch; GP = patient group. *From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.

al,[13] in a detailed analysis of side effects, recorded a higher incidence of nausea and vomiting (30%–70%) and other side effects in both TTS-fentanyl and placebo groups. Respiratory depression, the potentially most serious problem, was also reported in several of the studies[7, 13, 18, 22, 38, 41] (Table 4).

We have performed a pilot clinical trial of two TTS-fentanyl patches to assess the analgesic effectiveness and safety of the system in posthysterectomy patients before the performance of a larger definitive study.[41, 42] In this study 20 patients (ASA 1–2) undergoing abdominal hysterectomy were entered into a randomized, double-blind, placebo-controlled trial comparing two dosage levels of TTS-fentanyl. Group I (placebo, N = 8), were treated with nonopioid TTS patches. Group II (N = 6) were treated with a TTS-fentanyl 50 patch, and group III (N

Table 4. TRANSDERMAL THERAPEUTIC SYSTEM WITH RESPIRATORY DEPRESSION IN COMPARATIVE STUDIES

	Incidence			
Study	Active	Placebo	Description	Treatment
Gourlay (1989)	$\frac{3}{13}$	—	SRR (Ward)	1 patient, naloxone 2 patients, O_2 mask Dose reduced
Duthie (1988)	$\frac{2}{9}$	—	SRR (Ward)	TTS-fentanyl removed
Plezia (1988)	$\frac{3}{22}$	$\frac{1}{21}$	AP (PACU) SRR (Ward)	2 patients, naloxone TTS-fentanyl removed
Caplan (1989)	$\frac{3}{22}$	$\frac{0}{20}$	SRR (Ward)	Patients aroused
v. Bormann (1988)	$\frac{1}{20}$	$\frac{0}{20}$	SRR (Ward)	1 patient, naloxone TTS-fentanyl removed
Sandler (1991)	$\frac{8}{12}$	$\frac{0}{8}$	AP (Ward) SRR (Ward) DESAT (Ward)	O_2 mask

Abbreviations: SRR = slow respiratory rate (<10/min); AP = apneic episodes; DESAT = hemoglobin desaturation (<90%); Ward = SRR or AP occurring when patient returned to the ward; PACU = SRR or AP occurring in postanesthetic care unit. *From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.

= 6) with a TTS-fentanyl 75 patch. Blinding was achieved by applying the two-different sized patches (active or placebo) to all patients, producing the required fentanyl/placebo combinations. TTS patches were applied 2 hours preoperatively after diazepam premedication. Patients were given a standard general anesthetic, including sufentanil, 0.5 μg/kg, thiopentone, 3 to 5 mg/kg, pancuronium, 0.1 mg/kg, N_2O, and isoflurane. Postoperatively on the ward, all patients used a morphine-loaded patient-controlled analgesia device as required for supplementary analgesia. In the PACU patients were prompted at 5- to 10-minute intervals for intravenous morphine supplementation (1–2 mg) if in pain. Patients were monitored continuously by trained nursing personnel for 72 hours after patch application and for 12 hours after patch removal. Analgesia was assessed by VAS (VAS 0 = no pain, 10 = maximum pain) and hourly morphine requirement. Respiratory effects were monitored continuously with respiratory inductive plethysmography and pulse oximetry for 8 hours preoperatively the night before surgery and 84 hours postoperatively. The use and calibration of the respiratory inductive plethysmograph have been described elsewhere.[40, 43] Slow respiratory rate was defined as less than 10 breaths per minute for 5 minutes and apnea as tidal volume less than 100 mL for 15 seconds or longer. Arterial blood gases were drawn (under local anesthesia) if repeated episodes of hemoglobin desaturation less than 90% or respiratory rate less than 8/min occurred (Table 5). On analysis of the data there were no significant differences between groups for age, weight, height, or duration of surgery. There were no significant differences between groups for the four hourly VAS scores although there was a tendency for group III patients to have the lowest VAS scores (Fig. 4). Also, there were no significant differences in morphine requirements between groups in the PACU either (hour 1 = 10–15 mg per patient, hours 2, 3 = 2–10 mg per patient), although group III required much less morphine than the other two groups.

Table 5. TRANSDERMAL THERAPEUTIC SYSTEM WITH FENTANYL FOR POSTHYSTERECTOMY ANALGESIA: ARTERIAL BLOOD GAS MEASUREMENTS

Placebo (N = 0)			**TTS-Fentanyl 50 (N = 3)**		**TTS-Fentanyl 75 (N = 5)**	
Group	**Time (h)**	**pH**	**$PaCO_2$**	**PaO_2**	**HCO_3**	**Reason**
TTS-75	9.9	7.36	48	63	29	RR
TTS-75	34	7.38	42	59	26	O_2sat
TTS-75	24	7.41	46	61	29	RR/O_2sat
TTS-75	13	7.35	47	78	27	RR
TTS-75	27	7.42	47	63	30	O_2sat
TTS-50	29	7.37	47	67	28	O_2sat
TTS-50	10	7.31	53	71	27	RR
TTS-50	8	7.34	48	71	26	RR

Abbreviations: RR = respiratory rate; O_2 sat = hemoglobin saturation less than 90%; Time = time after TTS-fentanyl application.

See text for discussion of Table 5.

From Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.

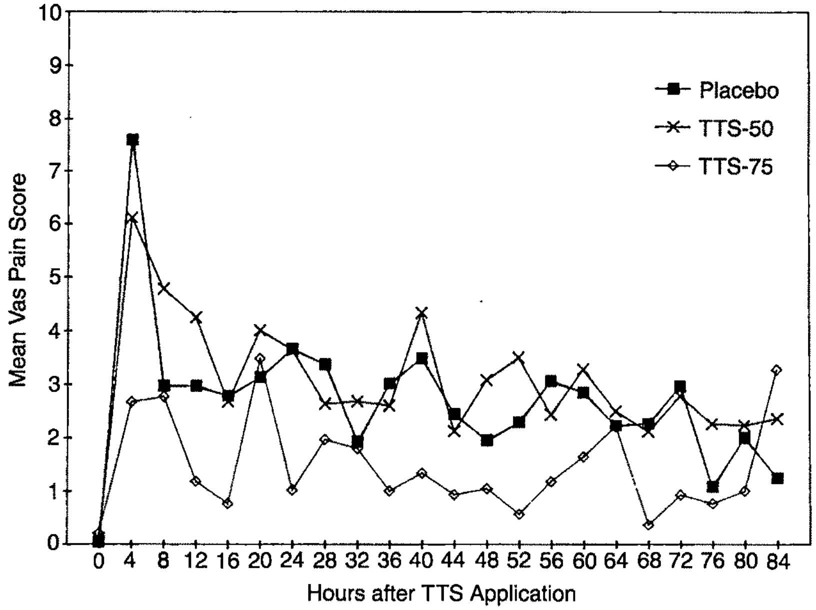


Figure 4. Mean four-hourly VAS pain scores in posthysterectomy patients enrolled in a pilot double-blind, placebo-controlled trial of TTS-50 and TTS-75 fentanyl patches. The high VAS scores at 4 hours denote the period in the PACU. TTS-75 fentanyl patients tended to have the lowest VAS scores. (*From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.)

Similarly, although there were no significant between-group differences in morphine requirements on the ward (probably related to the small sample sizes), group II (TTS-50) and group III (TTS-75) patients tended to use less patient-controlled analgesia morphine (Fig. 5). There were significantly more episodes of slow respiratory rate in the first 24 hours postoperatively in the TTS-fentanyl groups (Fig. 6) and a tendency to more episodes of apnea in the TTS-fentanyl up to 36 hours postoperatively (Fig. 7). Hemoglobin saturation also decreased more prominently in the TTS-fentanyl groups early in the postoperative period, although these changes were not statistically significant (Fig. 8). Eight patients, all in the TTS-fentanyl groups, required arterial blood gas determination for the criteria described previously (Table 5). This pilot study found similar results to the other comparative studies discussed previously, but also has indicated that the early postoperative period may be the time when patients are most vulnerable to respiratory depression with TTS-fentanyl patches. This problem may be decreased if the TTS-fentanyl patch is applied earlier than 2 hours preoperatively, thus possibly decreasing the supplementary opioid analgesic requirements in the PACU. A further, definitive, large-scale study similar to the pilot study is currently underway in our institution.

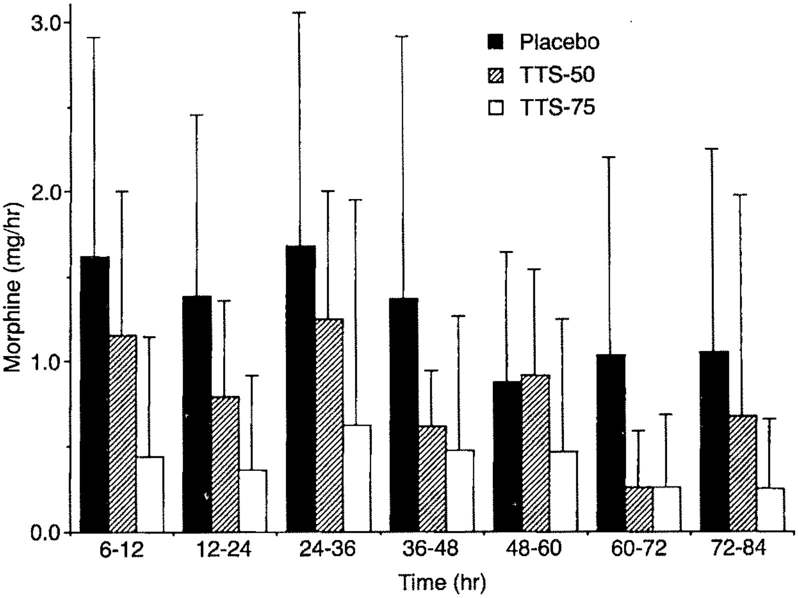


Figure 5. Hourly morphine requirements (mean ± SD) in posthysterectomy patients enrolled in a pilot double-blind, placebo-controlled trial of TTS-50 and TTS-75 fentanyl patches.[41, 42] The placebo group used PCA morphine alone and tended to have uniform morphine requirements for the 72-hour postoperative monitoring period, whereas the TTS fentanyl groups had reduced requirements. (*From* Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press; with permission.)

CONCLUSION

TTS-fentanyl patches are probably as efficacious as intravenous infusions of the same dose at the same delivery rate[29] but lack the rapid adjustability of intravenous infusions. In addition, many patients will require small amounts of analgesic supplementation while the patch is in situ. The application of the patch 2 hours preoperatively requires the administration of relatively large amounts of opioid analgesic in the PACU and this *may* be a contributing factor to early postoperative respiratory depression. Nimmo[37] has summarized the advantages and the disadvantages of the TTS-fentanyl patch as follows: advantages include ease of use, physician controlled, high patient acceptability, effective analgesic method, and nonlabor intensive; disadvantages include nontitratable, preselected dose, slow onset and preoperative patch application, requirement for supplemental analgesic, especially in PACU, and possible (although unlikely) toxic effects after patch removal. Nimmo[37] emphasizes and we agree that there is a need for the same nursing monitoring used for the same dose of systemic opioid given by any alternative route when TTS-fentanyl patches (or any form of effective opioid analgesic technique) are used.

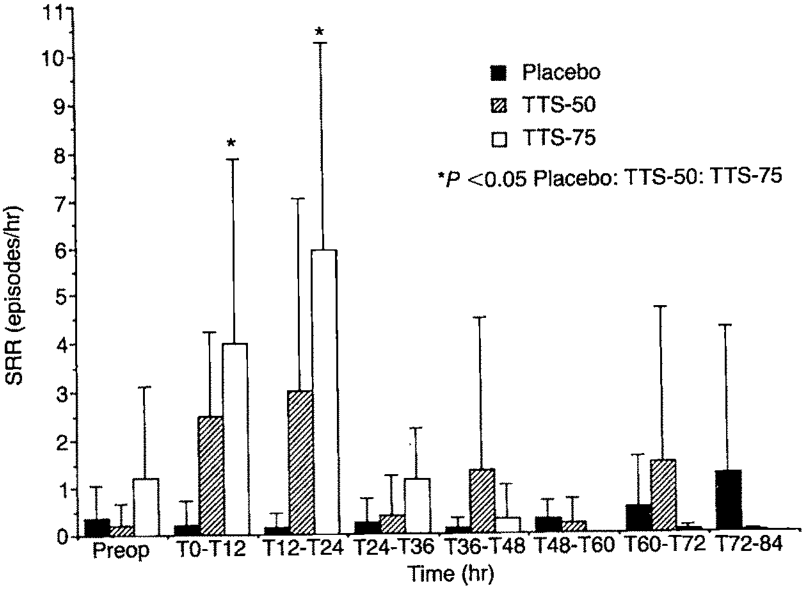


Figure 6. Episodes of SRR (mean ± SD, see text) in posthysterectomy patients enrolled in a pilot double-blind, placebo-controlled trial of TTS-50 and TTS-75 fentanyl patches.[41, 42] There were more SRR episodes in the TTS fentanyl groups in the first 24 hours postoperatively, especially in the TTS-75 fentanyl group.

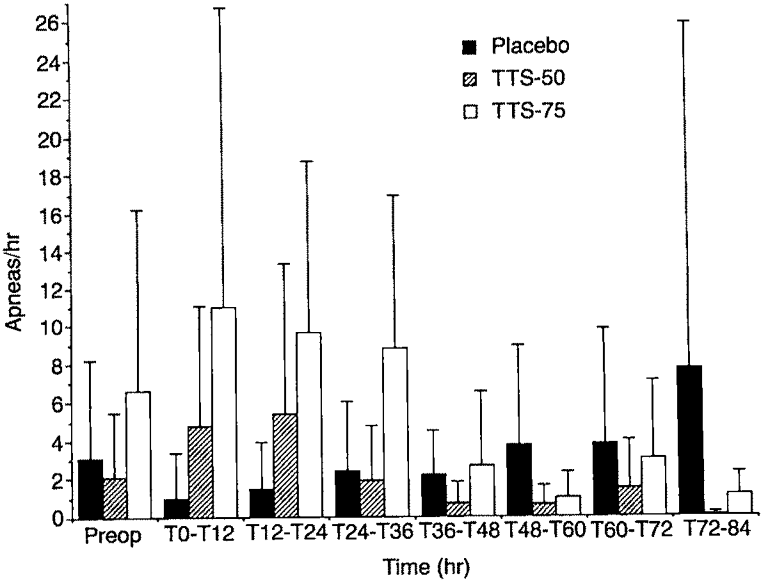


Figure 7. Apneic episodes (mean ± SD, see text) in posthysterectomy patients enrolled in a pilot double-blind, placebo-controlled trial of TTS-50 and TTS-75 fentanyl patches.[41, 42] The TTS fentanyl groups tended to have more apneic episodes in the first 24 to 36 hours postoperatively.

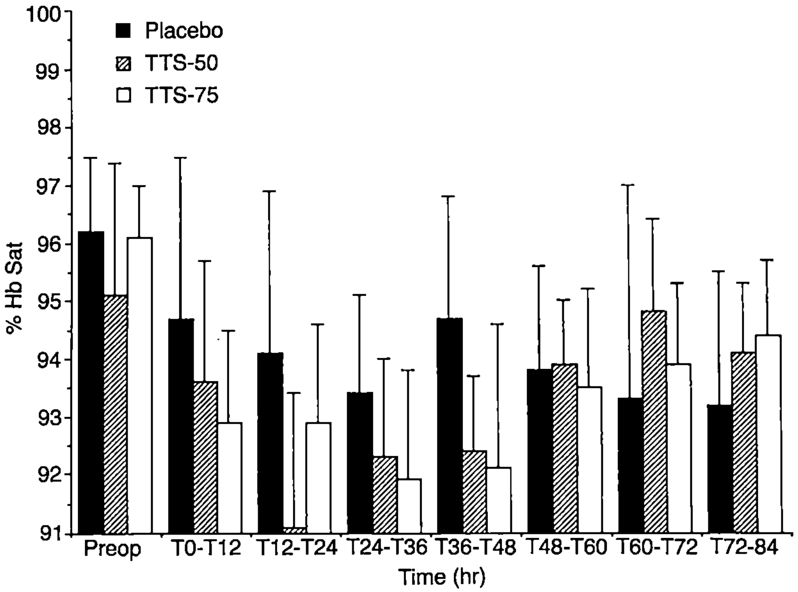


Figure 8. Hemoglobin saturation (mean ± SD, see text) in posthysterectomy patients enrolled in a pilot double-blind, placebo-controlled trial of TTS-50 and TTS-75 fentanyl patches.[41,42] Hemoglobin saturation was lower in the TTS fentanyl groups for up to 48 hours postoperatively.

SUMMARY

Current investigation is evaluating several novel techniques of opioid administration for acute (postoperative) analgesia. The underlying concept is to mimic a continuous intravenous infusion and provide stable, nontoxic, therapeutic plasma concentrations for prolonged periods in a simple, easy-to-use fashion. The promising techniques that are currently or likely to be widely available in the near future include buccal and sublingual opioids (morphine, buprenorphine), rectal hydrogel suppositories (morphine), and transdermal opioids (fentanyl, sufentanyl).

References

1. Bell MDD, Mishra P, Weldon BD, et al: Buccal morphine: A new route for analgesia. Lancet 1:71, 1985
2. Bell SD, Goldberg ME, Larijani GE, et al: Evaluation of transdermal fentanyl for multi-day analgesia in postoperative patients. Anesth Analg 68:S22, 1989
3. Bell SD, Goldberg ME: Comparison of single patch multi-day versus multiple patch single day TTS fentanyl. Can J Anaesth 36:S116, 1989
4. Bell SD, Larijani GE, Goldberg ME, et al: Evaluation of transdermal fentanyl for multi-day analgesia in postoperative patients. Anesthesiology 69:A362, 1988
5. Boas RA, Villiger JW: Clinical actions of fentanyl and buprenorphine. Br J Anaesth 57:192, 1985

6. Bogaert MG: Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. Clin Pharmacokinet 12:1, 1987
7. Bormann B. v., Ratthey K, Schwetlick G, et al: Postoperative schmerztherapie durch transdermales fentanyl. Anasth Intensivther Notfallmed 23:3, 1988
8. Brook-Williams P, Hoover LH: Morphine suppositories for intractable pain. Can Med Assoc J 126:14, 1982
9. Brown AS: Absorption of analgesics from the buccal mucous membrane. Practitioner 196:125, 1966
10. Bullingham RES, McQuay HJ, Dwyer D, et al: Sublingual buprenorphine used postoperatively: Clinical observations and preliminary pharmacokinetic analysis. Br J Clin Pharmacol 12:117, 1981
11. Bullingham RES, McQuay HJ, Porter EJB, et al: Sublingual buprenorphine used postoperatively: Ten hour plasma drug concentration analysis. Br J Clin Pharmacol 13:665, 1982
12. Bullingham RES, O'Sullivan G, McQuay HJ, et al: Mandatory sublingual buprenorphine for postoperative pain. Anaesthesia 39:329, 1984
13. Caplan RA, Ready LB, Oden RV, et al: Transdermal fentanyl for postoperative pain management. A double blind placebo study. JAMA 261:1036, 1989
14. Caplan RA, Southam M: Transdermal drug delivery and its application to pain control. *In* Benedetti C, Chapman RC, Giron G (eds): Advances in Pain Research and Therapy, vol 14. New York, Raven Press, 1990, p 233
15. Carl P, Crawford M, Madsen N, et al: Pain relief after major abdominal surgery: A double blind controlled comparison of sublingual buprenorphine, intramuscular buprenorphine and intramuscular meperidine. Anesth Analg 66:142, 1987
16. Cuschieri R, Morran C, McArdle C: Comparison of morphine and sublingual buprenorphine following abdominal surgery. Br J Anaesth 56:855, 1984
17. Derbyshire DR, Vater M, Maile CID, et al: Non-parenteral postoperative analgesia. Anaesthesia 39:324, 1984
18. Duthie DJR, Rowbotham DJ, Wyld R, et al: Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth 60:614, 1988
19. Edge WG, Cooper GM, Morgan M: Analgesic effects of sublingual buprenorphine. Anaesthesia 34:463, 1979
20. Fisher AP, Fung C, Hanna M: Absorption of buccal morphine. Anaesthesia 43:552, 1988
21. Fry ENS: Relief of pain after surgery—A comparison of sublingual buprenorphine and intramuscular papaveretum. Anaesthesia 43:549, 1979
22. Gourlay GK, Kowalski SR, Plummer JL, et al: The transdermal administration of fentanyl in the treatment of postoperative pain: Pharmacokinetics and pharmacodynamic effects. Pain 37:193, 1989
23. Hambrook JM, Rance MJ: The interaction of buprenorphine and the opiate receptor: Lipophilicity as a determining factor in drug receptor kinetics. *In* Kosterlitz (ed): Opiates and Endogenous Opioid Peptides. Elsevier, Amsterdam, 1976, p 259
24. Hanning CD, Vickers AP, Smith G, et al: The morphine hydrogel suppository: A new sustained release rectal preparation. Br J Anaesth 61:221, 1988
25. Hanning CD: The rectal absorption of opioids. *In* Benedetti C, Chapman RC, Giron G (eds): Advances in Pain Research and Therapy, vol 14. New York, Raven Press, 1990, p 259
26. Harris AS, Westerling D, Andersson KE: Rectal application of morphine. Br J Pharm Pract 4:21, 1982
27. Hickey RF, Severinghaus JW: Regulation of breathing: drug effects. *In* Hornbein TF (ed): Lung Biology in Health and Disease: Regulation of Breathing, vol 17. New York, Dekker, 1981, p 1251
28. Hill HF: Clinical pharmacology of transdermal fentanyl. Eur J Pain 11:81, 1990
29. Holley FO, Van Steennis C: Postoperative analgesia with fentanyl: Pharmacokinetics and pharmacodynamics of constant-rate i.v. and transdermal delivery. Br J Anaesth 60:608, 1988
30. Larijani GE, Bell SD, Goldberg ME, et al: Pharmacokinetics of fentanyl following transdermal application. Anesthesiology 69:363A, 1988
31. Laufer LR, DeFazio JL, Lu KJH, et al: Estrogen replacement therapy by transdermal estradiol administration. Am J Obstet Gynecol 146:533, 1983

32. Maunuksela E, Korpela R, Olkkola K: Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. Anesth Analg 67:233, 1988
33. McLeskey CH: Fentanyl TTS for postoperative analgesia. Eur J Pain 11:92–97, 1990
34. Mroczek WJ, Ulrych M, Yoder S: Weekly transdermal clonidine administration in hypertensive patients. Clin Pharmacol Ther 31:352, 1982
35. Nairn JG: Transdermal therapeutic systems: Some fundamental considerations. Can J Hosp Pharm 41:85, 1988
36. Nelson PS, Streisand JB, Mulder S, et al: Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine for premedication in children. Anesthesiology 70:616, 1989
37. Nimmo WS: Clinical summary: Transdermal fentanyl. Eur J Pain 11:102, 1990
38. Plezia PM, Linford J, Kramer TH, et al: Transdermally administered fentanyl for postoperative pain: A randomized double blind placebo controlled trial. Anesthesiology 69:A364, 1988
39. Rowbotham DJ, Wyld R, Peacock JE, et al: Transdermal fentanyl for the relief of pain after upper abdominal surgery. Br J Anaesth 63:56, 1989
40. Sackner MA, Watson H, Belsito AS, et al: Calibration of respiratory inductive plethysmograph during natural breathing. J Appl Physiol 66:410, 1989
41. Sandler AN, Baxter AD, Norman P, et al: A double blind, placebo-controlled trial of transdermal fentanyl for posthysterectomy pain relief. II. Respiratory effects. Can J Anaesth 38:A114, 1991
42. Sandler AN: Transdermal fentanyl: Acute analgesic clinical studies. Journal of Pain and Symptomatic Management 1992, in press
43. Sandler AN, Chovaz P, Whiting W: Respiratory depression following epidural morphine: A clinical study. Can Anaesth Soc J 33:542, 1986
44. Shah MV, Jones DI, Rosen M: "Patient demand" postoperative analgesia with buprenorphine: Comparison between sublingual and i.m. administration. Br J Anaesth 58:508, 1986
45. Tarver SD, Stanley TH: Alternative routes of drug administration and new drug delivery systems. *In* Stoelting RK, Barash P, Gallagher TJ (eds): Advances in Anesthesia, vol 7. Chicago, Year Book Medical, 1990, p 337
46. Twycross R: Relief of pain. *In* Saunders X (ed): The Management of Terminal Disease. London, Edward Arnold, 1978, p 65
47. Uppington J, Dunnet J, Blogg CE: Transdermal hyoscine and postoperative nausea and vomiting. Anaesthesia 41:16, 1986
48. Varvel JR, Shafer SL, Hwang SS, et al: Absorption characteristics of transdermally administered fentanyl. Anesthesiology 70:928, 1989
49. Vercauteren M, Boeckx E, Hanegreefs G, et al: Intranasal sufentanil for preoperative sedation. Anaesthesia 43:270, 1988
50. Westerling D: Rectally administered morphine: Plasma concentrations in children premedicated with morphine in hydrogel and in solution. Acta Anaesth Scand 28:540, 1984

Address reprint requests to

Alan N. Sandler, MB ChB
Department of Anesthesiology
Toronto General Hospital
GW2-502
Toronto, Ontario
Canada M5G 2C4

CURRENT CONCEPTS IN ACUTE PAIN CONTROL 0889–8537/92 $0.00 + .20

PATIENT-CONTROLLED ANALGESIA

F. Michael Ferrante, MD

A HISTORICAL PERSPECTIVE

The first demonstration of a patient-controlled analgesia (PCA) infuser in the United States occurred in 1984. Since that time, there has been a veritable explosion of interest in PCA as an analgesic modality. This interest in PCA, and more effective postoperative analgesia in general, is not related to the development of new and better analgesic agents. Rather, it is the appreciation that PCA represents a more optimal mode of administration of perfectly adequate analgesic agents. The factors responsible for this reappraisal of traditional modes of analgesic administration are both scientific and economic:

1. The intramuscular administration of opioids on a pro re nata or fixed time schedule cannot provide uniform analgesia or consistent analgesic blood levels in the majority of patients. This is simply the result of the pharmacokinetic properties of opioids.
2. Novel bioengineering and new technology have allowed the development of sophisticated, safe, "user-friendly" infusion devices. Such devices remove the logistic difficulties of administration of small doses of intravenous opioids at frequent intervals by health professionals.
3. Nonphysician health care providers, i.e., hospital administrators and insurance companies, are increasingly interested in cost containment. Improvements in postoperative analgesia can

---

From the Pain Management Center, Department of Anesthesia, Brigham and Women's Hospital; and Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts

potentially reduce the morbidity and length of stay of surgical patients, resulting in significant cost reductions.

Thus, intravenous PCA stands increasingly poised to supplant intramuscular opioids as the mainstay of analgesic therapy.

Before discussion of intravenous PCA with opioids, it is important to note that PCA is much more than a modality. In a much broader sense, PCA is a conceptual framework for the administration of analgesics. The average practitioner assumes the term *PCA* to imply the on-demand, intermittent, intravenous administration of opioids. The broader concept of PCA is not restricted to a single class of analgesics or single route or mode of administration (Table 1). Any analgesic given by any route of administration (e.g., oral, subcutaneous, or epidural) can be deemed to be PCA if administration is on immediate patient demand in plentiful quantities.

With this important clarification now made, I begin the discussion of intravenous PCA by explaining the problems inherent in the use of traditional analgesic regimens.

TRADITIONAL ANALGESIC REGIMENS

The barriers to satisfactory analgesia with traditional intramuscular or continuous intravenous opioid regimens are twofold: (1) pharmacokinetic and (2) educational and attitudinal.

The Patient-Controlled Analgesia Paradigm

Opioid analgesia is achieved when the plasma concentrations reach a specific effective level distinct for the individual patient (MCP, Fig. 1). For a small increase in plasma concentration, there is a rapid decrease in the appreciation of pain. The nadir of the perceived pain defines the minimal effective analgesic concentration (MEAC). For concentrations above MEAC, there is no further increase in the intensity of analgesia.

Table 1. PATIENT-CONTROLLED ANALGESIA AS AN ANALGESIC CONCEPT

Classes of analgesics	Modes of administration
Benzodiazepines[30]	Demand dosing[16, 34]
Local anesthetics[16, 19, 20, 31]	Infusion-based systems[25]
Opioids[3, 7, 12, 15, 17, 22, 24, 26, 35, 36]	Constant-rate infusion plus demand dosing[34, 36]
Routes of administration	
Epidural[16, 19, 20, 31, 33]	
Intravenous[3, 7, 12, 15, 17, 22, 24, 26, 35]	
Subcutaneous[47, 50]	
Sublingual[41]	
Transbuccal[5]	

Use of PCA does not imply the use of opioids or the intravenous route of administration.

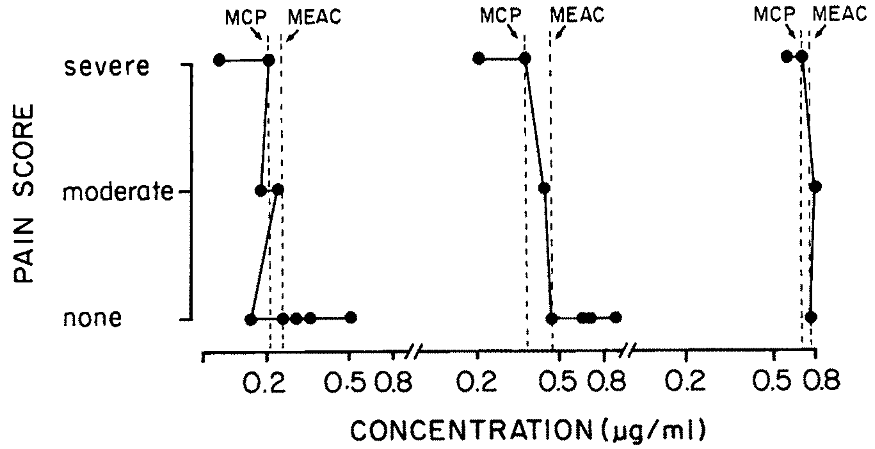


Figure 1. The relation between plasma concentration of opioid and analgesia. For a minimal increase in opioid concentration above the maximum concentration associated with severe pain (MCP), there is a rapid decrease in pain. The nadir of the perceived pain is called the minimum effective analgesic concentration (MEAC). (*From* Austin KL, Stapleton JV, Mather LE: Relationship between blood meperidine concentrations and analgesic response: A preliminary report. Anesthesiology 53:460, 1980; with permission.)

For small decreases in concentration below MEAC, there is rapid appreciation of pain. MEAC exhibits considerable interpatient variability, perhaps explaining the large clinically observed interpatient variability of analgesic requirements.[2]

The relation among plasma opioid concentration, analgesia, and dosing interval defines the therapeutic effectiveness of a particular modality of opioid administration (Fig. 2) (excluding administration of opioids directly to the neuraxis). Intramuscular injections characteristically yield unpredictable plasma concentrations. With multiple intramuscular injections, individual peak concentrations can vary twofold. Similarly, time to peak concentration can vary threefold.[1] Within any population of patients, peak concentrations can vary fivefold while time to peak concentrations can vary sevenfold.[1] At the same time, plasma concentrations will fluctuate in phase with the dosing interval (Fig. 2). Calculations reveal that opioid concentrations exceed MEAC only 35% of the time during any 4-hour dosing interval.[1]

Continuous intravenous infusions of opioids do improve controllability and prevent fluctuating opioid concentrations.[9, 40, 43] It is the natural history of postoperative pain that pain attendant from the operation decreases as time progresses. With continuous opioid infusions in the postoperative setting, frequent and repeated adjustments of the infusion rate are necessary because of the natural history of the pain and individual pharmacodynamics. Without frequent infusion rate adjustments, respiratory depression will occur with continuous infusion modalities used for postoperative analgesia. Continuous opioid infusions are better suited for situations in which the natural history of pain is relatively static (cancer pain).

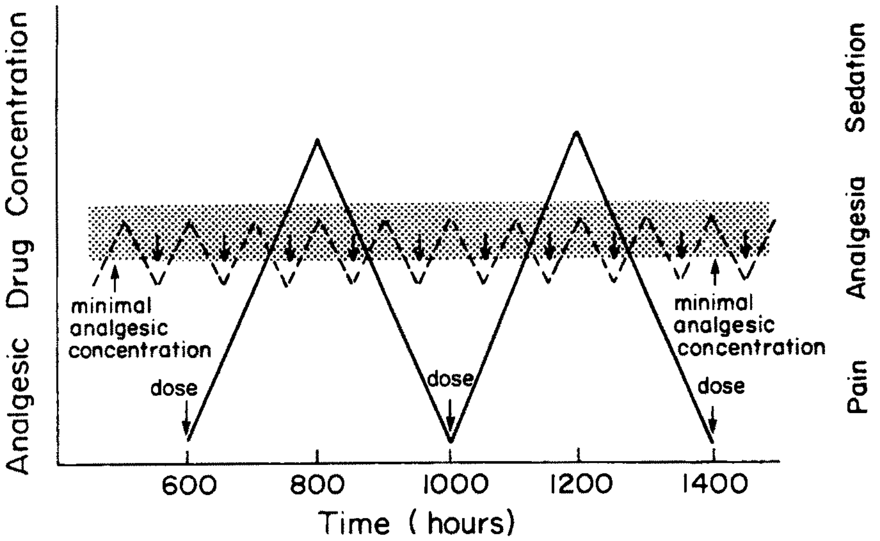

Analgesic Drug Concentration
Sedation
Analgesia
Pain
minimal analgesic concentration
dose
dose
minimal analgesic concentration
dose
600
800
1000
1200
1400
Time (hours)

Figure 2. The PCA paradigm. A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. (*From* Ferrante FM, Orav EJ, Rocco AG, et al: A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 67:457–461, 1988; with permission of the International Anesthesia Research Society.)

PCA avoids the variable absorption phenomena of intramuscular opioids and the logistical difficulties of frequent infusion rate adjustment with intravenous infusions. PCA allows on-demand, repetitive dosing of small amounts of opioids by the patient. When the patient's plasma concentration falls below MEAC, the patient rapidly appreciates pain (steep concentration-analgesic response relation). Thus, patients use PCA to titrate their plasma concentration of opioid around MEAC. PCA provides more constant plasma levels of opioid[12, 44, 45] and more consistent analgesia.[17]

Educational and Attitudinal Problems

Knowledge deficits regarding opioid pharmacology and the attitudes of health care professionals about the goals of analgesic therapy form the second barrier to satisfactory analgesia with conventional opioid regimens. While the literature is replete with studies demonstrating this knowledge deficit,[10, 11, 13, 27–29, 37] the study of Marks and Sachar[32] represents the most telling indictment. In what is now a classic study, 32% of patients experienced severe pain despite provision of an analgesic regimen. Another 41% reported moderate distress. Physicians possessed significant misinformation and demonstrated an appreciable lack of sophistication regarding effective use of analgesics. Many physicians underestimated the effective dose range, overestimated the duration of action, and exaggerated the dangers of respiratory depression and addiction for patients receiving meperidine in a therapeutic dose range.[32]

With an appreciation of the problems inherent in the use of more traditional opioid regimens, let us now explore the pharmacology of patient-administered opioids.

INTRAVENOUS PATIENT-CONTROLLED ANALGESIA

Definition of Patient-Controlled Analgesia Modes and Dosing Parameters

There are several modes of administration of PCA. Demand dosing is most commonly used. (A dose of fixed size is intermittently administered by the patient.) A background constant-rate infusion can also be used to supplement patient demand (constant-rate infusion plus demand dosing). Increasing the background infusion rate places the technique more in the category of physician-controlled rather than patient-controlled analgesia. Less commonly available modes include infusion demand (where demands are granted as an infusion) and variable-rate infusion plus demand dosing (where a microprocessor monitors demands and controls the infusion rate accordingly). These infusion-based systems are not widely available and need to be studied further.

For each PCA mode, there are basic variables: loading dose, demand dose, lockout interval, background infusion rate, and 1- and 4-hour limits. Loading dose is the cumulative amount of opioid used to initially make the patient analgesic. The demand dose (incremental or PCA dose) is the quantity of analgesic given to the patient by self-administration on the perception of the need for additional analgesic. The lockout interval is the absolute time period between patient demands wherein the infuser will not administer analgesics. Provision of a lockout interval prevents overdosage by continual demand. Some PCA infusers allow provision of 1- and 4-hour limits, though the use and necessity of such limits is controversial.

Any opioid can be administered under patient control. Guidelines for administration of several commonly used opioids are listed in Table 2. Unfortunately, the development of guidelines for opioid administration with PCA has been largely empiric. Much research is needed into the scientific basis for the choice of basic administration parameters.[35, 36]

Individual Analgesic Requirements

PCA is a dynamic, flexible modality because it allows patients to take as little, or as much, opioid as they desire. Therefore, PCA can accommodate patients' widely divergent analgesic requirements. With PCA, individual differences in analgesic requirements are expressed in

Table 2. GUIDELINES FOR THE USE OF PATIENT-CONTROLLED ANALGESIA WITH SEVERAL COMMON OPIOIDS

Drug (concentration)	Demand Dose	Lockout Interval (min)
Fentanyl (10 μg/mL)	10–20 μg	5–10
Hydromorphone (0.2 mg/mL)	0.05–0.25 mg	5–10
Meperidine (10 mg/mL)	5–30 mg	5–12
Methadone (1 mg/mL)	0.5–2.5 mg	8–20
Morphine (1 mg/mL)	0.5–3.0 mg	5–12
Nalbuphine (1 mg/mL)	1–5 mg	5–10
Oxymorphone (0.25 mg/mL)	0.2–0.4 mg	8–10

Analgesic requirements vary widely among patients. Age, the presence of severe disease, or the idiosyncrasies of individual drug handling may make dosage adjustment necessary.

individual patterns of analgesic administration. Thus, by understanding the pharmacokinetic and pharmacodynamic factors affecting analgesic requirements, we can understand how patients may effectively (or ineffectively) use PCA.

Pharmacokinetic Factors

The contribution of pharmacokinetics on analgesic requirements in patients using PCA was studied by Tamsen and coworkers[12, 44, 45] in a classic series of articles. The volume of distribution, distribution rate constant, and elimination rate constant for meperidine,[45] ketobemidone,[44] and morphine[12] were studied in patients undergoing laparotomy. Pharmacokinetic parameters were found to have no relation to an individual's hourly analgesic requirement. Pharmacokinetic variations among patients had no influence on patients' hourly demand for opioid using PCA. Mean plasma opioid concentration and MEAC, however, were found to significantly correlate with individual hourly opioid use.

Pharmacodynamic Factors

All opioids produce analgesia by mimicking the actions of endogenous opioids.[18] Thus, changes in levels of endogenous opioids or changes in opioid receptor numbers or affinities could influence analgesic requirements. Tamsen and coworkers[46] examined the impact of CSF preoperative endogenous opioids on postoperative analgesic requirement. Before laparotomy, lumbar puncture was performed and a sample of CSF was obtained. Endogenous opioid content was determined using a radioreceptor assay. Patients received a standardized anesthetic and meperidine via PCA for postoperative analgesia. Another sample of CSF, as well as a sample of central venous blood, was obtained 24 hours after surgery while patients used PCA. The concentration of meperidine was determined in these specimens.

A significant inverse relation was discovered between preoperative endogenous opioid concentrations in the CSF and individual postoperative concentrations of meperidine in plasma ($r^2 = 0.29$, $P < 0.05$) and in CSF ($r^2 = 0.43$, $P < 0.03$) (Fig. 3).[46] Patients with low preoperative endogenous opioid content in CSF administered more opioids postoperatively by PCA in order to maintain higher concentrations in the plasma. Similarly, the converse was true.

Tamsen et al[46] hypothesized that endogenous opioids interact with exogenously administered opioids to influence analgesic demand and MEAC. The results of this study state that individual analgesic demand is dictated by individual CSF endogenous opioid content. While compelling, this contention is probably an oversimplified explanation of complex neurochemical and neurophysiologic events. If true, use of PCA would be "physiologic." Recently, the results of Tamsen et al[46] have been questioned.[14]

Psychological Factors

If CSF endogenous opioid levels were the only determinant of how patients use PCA, PCA would be flawlessly efficacious ("physiologic theory") in all patients. Patients would be machines, passively responding to CSF opioid concentrations. A patient's decision to press or not to press the demand button remains paramount irrespective of phar-

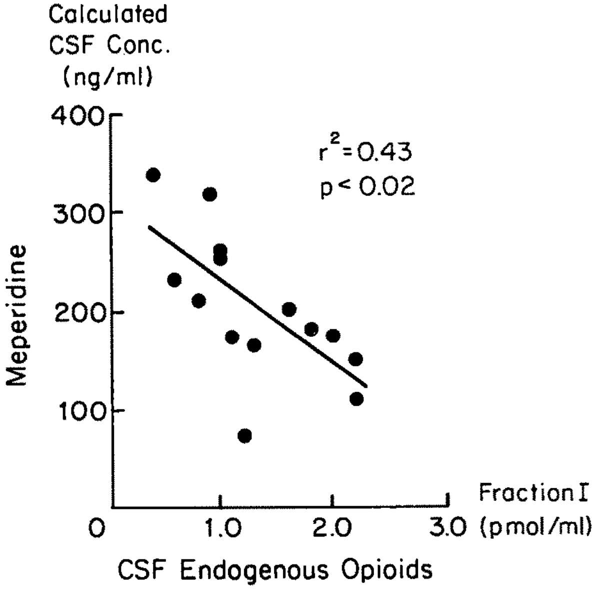


Figure 3. The inverse linear relationship between preoperative CSF levels of endogenous opioids (fraction I) and postoperative analgesic demand (CSF concentration of meperidine) while using PCA. (*From* Ferrante FM, Ostheimer GW, Covino, BG: Patient-Controlled Analgesia. Boston, 1990, p. 56; by permission of Blackwell Scientific Publications, Inc.)

macokinetic and pharmacodynamic considerations. Thus, the myriad factors of an individual's psyche are involved in how a particular patient uses PCA.

A basic tenet of PCA is that analgesia is more effective when the patient is in control, not the medical or nursing staff. The psychological construct of "locus of control"[38, 39, 48] refers to a set of beliefs about the relation between behavior and subsequent reinforcement. Patients with an internal locus of control perceive their health to be largely the result of their own actions. Patients with an internal locus of control adopt a more active, dynamic posture toward their environment. On the other hand, if patients believe that luck, chance, fate, or the intervention of powerful people (doctors and nurses) play more of a role in determining their health than their own actions, they are said to possess an external locus of control. Such individuals would be expected to adopt a more passive attitude toward their environment. A passive attitude toward pain or pain relief may make the patient unable to control his or her own analgesia effectively.

Another psychological construct that may be important in determining how effectively patients use PCA is "learned helplessness."[21] Learned helplessness refers to a behavioral pattern characterized by emotional, motivational, and cognitive deficits in coping, associated with the belief that no effective solutions are available to ameliorate a source of stress (such as pain). Learned helplessness may also lead to a paralysis of response and inability to effectively use PCA.

Pain and satisfaction associated with use of PCA have been correlated with the results of psychometric testing using multiple regression analyses.[26] External locus of control did correlate with greater pain and dissatisfaction with PCA. The converse was also true.

Much further work is certainly needed to elucidate the psychological factors involved in effective use of PCA. At the present time, through the aforementioned work[26] and other recent studies,[22] we do know that psychometric testing is a viable tool to investigate factors that affect patients' ability to use PCA.

Safety

When examining the complications associated with PCA, the inherent safety of the modality is apparent. With approximately 50,000 devices currently in use in the United States, review of the literature reveals few complications associated with PCA as a distinct technique. Problems are usually attributable to the individual drugs being administered rather than the device itself.[8, 27, 28] All problems that have been documented with use of PCA can be classified into three groups: (1) adverse reactions and side effects (drug related), (2) mechanical problems, and (3) user-related problems.

Adverse Reactions and Side Effects

The incidence of nausea, vomiting, sweating, or pruritus associated with PCA is rarely greater than 10% to 20%. Ileus is reported, but it is difficult to distinguish opioid-induced ileus from other contributing variables (surgical technique, length of operation, type of surgery). In short, there is no evidence to suggest a greater incidence of these problems with use of PCA than with other techniques of opioid administration.[8]

Opioids cause progressive central respiratory depression manifested as displacement of the CO_2 response curve or a change in breathing pattern. Respiratory depression is dose-dependent, with equianalgesic dosages of opioids causing equivalent degrees of respiratory depression.[6] Clinically observed differences in the degree of respiratory depression are the result of the pharmacokinetics and pharmacodynamics of different opioids.[6, 34] Such differences will be nullified at equianalgesic dosages under controlled conditions. Thus, the total dosage of opioid over a specified period of time is more important in the production of respiratory depression than the particular opioid or the technique of PCA.[34]

Mechanical Problems

A review of Medical Device Reports of the Food and Drug Administration regarding PCA reveals that few problems are truly attributable to mechanical failure. User error is the cause of problems in 67% of cases. Almost all reports of "continued" delivery are associated with misprogramming of the PCA infuser.

Siphoning, however, is a mechanical problem. Excessive use of force in positioning the reservoir glass or plastic syringe can cause cracks in the reservoir. Build up of pressure within the reservoir can cause the crack to widen and entrain air into the system. This can lead to a constant flow of opioid into intravenous tubing and respiratory arrest.

With refinements in infuser design (antisiphon valves, changes in reservoir mounting design) the incidence of siphoning is greatly reduced. The incidence of cracked reservoirs in 1986 was 7.02 per 100,000. By 1987, this had been reduced to 1.45 per 100,000. Today, siphoning occurs because of user abuse of the system.

One fatality has been associated with use of PCA.[23] The reason for the apparent overdose has not yet been determined. Siphoning or a true "runaway" delivery may have occurred.

Machine–User Interface

As stated previously, misprogramming and user error are much more often associated with problems with PCA than machine failure. Two cases of misprogramming have been reported in the literature.[49]

No device is completely tamper-proof despite the best efforts of manufacturers. Patients desiring to tamper with PCA infusers can be quite ingenious. Instruments have been devised by patients to slip behind locked plexiglass doors to gain access to dose buttons or opioid itself. Access codes to infusers can be memorized by patients.[8]

What conclusions can we draw from this review of complications associated with PCA? PCA infuser technology is safe. The sophistication and safety of PCA infuser design has been one of the motivating forces in the rapid growth and acceptance of PCA.

SUMMARY

An appreciation of the inadequacies of traditional routes of opioid administration, coupled with the development of safe user-friendly infusion devices can partly account for the recent, rapid, widespread appeal of PCA. More importantly, PCA is uniformly more effective than traditional opioid regimens. Notwithstanding academic arguments regarding pharmacokinetics, pharmacodynamics, bioengineering, and economics, it is the tremendous patient satisfaction with PCA[15, 24] that really accounts for its widespread popularity. It is because of such widespread appeal that PCA is increasingly seen to supplant intramuscular opioids as the mainstay of postoperative analgesic therapy.

References

1. Austin KL, Stapleton JV, Mather LE: Multiple intramuscular injections: A major source of variability in analgesic response to meperidine. Pain 8:47, 1980
2. Austin KL, Stapleton JV, Mather LE: Relationship between blood meperidine concentrations and analgesic response: A preliminary report. Anesthesiology 53:460, 1980
3. Babar M, Rosen M, Vickers MD: Self-administered nalbuphine, morphine and pethidine. Comparison by intravenous route, follow cholecystectomy. Anaesthesia 40:529, 1985
4. Banister EHD'A: Six potent analgesic drugs: A double-blind study in post-operative pain. Anaesthesia 29:158, 1974
5. Bell MD, Murray GR, Mishin P, et al: Buccal morphine—A new route for analgesia? Lancet 1:71, 1985
6. Belleville JW, Seed JC: The effects of drugs on the respiratory response to carbon dioxide. Anesthesiology 21:727, 1960
7. Bollish SJ, Collins CL, Kirking DM, et al: Efficacy of patient-controlled versus conventional analgesia for postoperative pain. Clin Pharm 4:48, 1985
8. Callan CM: An analysis of complaints and complications with patient-controlled analgesia. *In* Ferrante FM, Ostheimer GW, Covino BG (eds): Patient-Controlled Analgesia. Boston, Blackwell Scientific, 1990, p 139
9. Church JJ: Continuous narcotic infusions for relief of postoperative pain. Br Med J 1:977, 1979
10. Cohen FL: Postsurgical pain relief: Patient's status and nurses' medication choices. Pain 9:265, 1980
11. Cronin M, Redfern PA, Utting JE: Psychometry and postoperative complaints in surgical patients. Br J Anaesth 45:879, 1973
12. Dahlström B, Tamsen A, Paalzow L, et al: Patient-controlled analgesic therapy, Part IV: Pharmacokinetics and analgesic plasma concentration of morphine. Clin Pharmacokinet 7:266, 1982

13. Donovan M, Dillon P, McGuire L: Incidence and characteristics of pain in a sample of medical-surgical inpatients. Pain 6:249, 1979
14. Eisenach JC, Dobson II CE, Inturrisi CE, et al: Effect of pregnancy and pain on cerebrospinal fluid immunoreactive enkephalins and norepinephrine in healthy humans. Pain 43:149, 1990
15. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. Anesthesiology 68:444, 1988
16. Ferrante FM, Lu L, Jamison SB, et al: Patient-controlled epidural analgesia: Demand dosing [abstract]. Reg Anesth 16:36S, 1991
17. Ferrante FM, Orav EJ, Rocco AG: A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 67:457, 1988
18. Fields HL: Central nervous system mechanisms for control of pain transmission. *In* Pain. New York, McGraw-Hill, 1987, p 99
19. Gambling DR, McMorland GH, Yu P, et al: Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. Anesth Analg 70:256, 1990
20. Gambling DR, Yu P, McMorland GH, et al: A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. Can J Anaesth 35:249, 1988
21. Garber J, Seligman MEP: Human helplessness: Theory and applications. New York, Academic Press, 1980
22. Gill KM, Ginsberg B, Muir M, et al: Patient-controlled analgesia in postoperative pain: The relation of psychological factors to pain and analgesic use. Clin J Pain 6:137, 1990
23. Grey TC, Sweeney ES: Patient-controlled analgesia [letter]. JAMA 259:2240, 1988
24. Harrison DM, Sinatra R, Morgese L, et al: Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. Anesthesiology 68:454, 1988
25. Hill HF, Mackie AM, Jacobson RC: Infusion-based patient-controlled analgesia systems. *In* Ferrante FM, Ostheimer GW, Covino BG (eds): Patient-Controlled Analgesia. Boston, Blackwell Scientific, 1990, p 214
26. Johnson LR, Magnani BJ, Chan V, et al: Modifiers of patient-controlled analgesia efficacy. I: Locus of control. Pain 39:17, 1989
27. Keats AS: Postoperative pain: Research and treatment. J Chron Dis 4:72, 1956
28. Keeri-Szanto M, Heaman S: Postoperative demand analgesia. Surg Gynecol Obstet 134:647, 1972
29. Lasagna L, Beecher HK: The optimal dose of morphine. JAMA 156:230, 1954
30. Loper KA, Ready LB, Brody M: Patient-controlled anxiolysis with midazolam. Anesth Analg 67:1118, 1988
31. Lysak SZ, Eisenach JC, Dobson II CE: Patient-controlled epidural analgesia during labor: A comparison of three solutions with a continuous infusion control. Anesthesiology 72:44, 1990
32. Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 78:173, 1973
33. Marlowe S, Englstrom R, White PF: Epidural patient-controlled analgesia (PCA): An alternative to continuous epidural infusions. Pain 37:97, 1989
34. Mather LE, Owen H: The pharmacology of patient-administered opioids. *In* Ferrante FM, Ostheimer GW, Covino BG (eds): Patient-Controlled Analgesia. Boston, Blackwell Scientific, 1990, p 27
35. Owen H, Plummer JL, Armstrong I, et al: Variables of patient-controlled analgesia: 1. Bolus size. Anaesthesia 44:7, 1989
36. Owen H, Szekeley SM, Plummer JL, et al: Variables of patient-controlled analgesia: 2. Concurrent infusion. Anaesthesia 44:11, 1989
37. Papper EM, Brodie BB, Rovenstine EA: Postoperative pain: Its use in comparative evaluation of analgesics. Surgery 32:107, 1952
38. Rotter JB: Generalized expectancies for internal versus external control of reinforcement. Psychol Monogr 80:1, 1966
39. Rotter JB: Some problems and misconceptions related to the construct of internal versus external locus of control of reinforcement. J Consult Clin Psychol 43:56, 1975

40. Rutter PC, Murphy F, Dudley HAF: Morphine: Controlled trial of different methods of administration for postoperative pain relief. Br Med J 1:12, 1980
41. Shah MV, Jones DI, Rosen M: "Patient demand" postoperative analgesia with buprenorphine. Comparison between sublingual and IM administration. Br J Anaesth 58:508, 1986
42. Sjöstrom S, Hartvig D, Tamsen A: Patient-controlled analgesia with extradural morphine or pethidine. Br J Anaesth 60:358, 1988
43. Stapleton JV, Austin KL, Mather LE: A pharmacokinetic approach to postoperative pain: Continuous infusion of pethidine. Anaesth Intens Care 7:25, 1979
44. Tamsen A, Bondesson V, Dahlström B, et al: Patient-controlled analgesic therapy. Part III. Pharmacokinetics and analgesic plasma concentrations of ketobemidone. Clin Pharmacokinet 7:252, 1982
45. Tamsen A, Hartvig P, Fagerlund C, et al: Patient-controlled analgesic therapy. Part II. Individual analgesic demand and analgesic plasma concentrations of pethidine in postoperative pain. Clin Pharmacokinet 7:164, 1982
46. Tamsen A, Sakurada T, Wahlström A, et al: Postoperative demand for analgesics in relation to individual levels of endorphins and substance P in cerebrospinal fluid. Pain 13:171, 1982
47. Urquhart ML, Klapp K, White PF: Patient-controlled analgesia: A comparison of intravenous versus subcutaneous hydromorphone. Anesthesiology 69:428, 1988
48. Wallston KA, Wallston BS, DeVillis R: Development of the Multidimensional Health Locus of Control (MHLC) Scales. Health Educ Monogr 6:160, 1978
49. White PF: Mishaps with patient-controlled analgesia. Anesthesiology 66:81, 1987
50. White PF: Subcutaneous-PCA: An alternative to IV-PCA for postoperative pain management. Clin J Pain 6:297, 1990

Address reprint requests to

F. Michael Ferrante, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115

NEW SYSTEMIC ANALGESIC AGENTS

Mark S. Shulman, MD

For centuries, opium and related alkaloids derived from opium have been the mainstay of analgesic therapy. Morphine, first isolated in 1806, is the gold standard by which all other analgesic agents are measured. Unfortunately, opioid analgesics have multiple well-known undesirable side effects.

An ideal analgesic for postoperative pain would provide reliable pain relief for all patients, without causing nausea, excessive sedation, dysphoria, tolerance, pruritus, respiratory depression, sensory or motor blockade, constipation, urinary retention, cardiovascular instability, or drug dependence in either patient or health care worker. No such agent currently exists, but attempts are continually being made to develop systemic and local drugs that are effective and have as few side effects and as little abuse potential as possible.

Several promising new analgesics are now available. One is dezocine, a short-acting μ-agonist-antagonist. Another is ketorolac, a nonsteroidal anti-inflammatory drug that inhibits prostaglandin synthesis and is a potent painkiller. α_2-Agonists, such as clonidine, have analgesic properties when administered systemically and epidurally. Capsaicin is a topical agent that depletes substance P from small C fibers, thereby providing cutaneous analgesia.

DEZOCINE

Dezocine is a potent analgesic agent with opioid agonist-antagonist activity. The drug, first synthesized in 1973, is a bridged aminotetralin

---

From the Department of Anesthesiology, Tufts University School of Medicine; and the Department of Anesthesiology, St. Elizabeth's Hospital of Boston, Boston, Massachusetts

with a structure similar to that of other agonist-antagonists, such as butorphanol and pentazocine (Fig. 1).

The mechanism of action of dezocine primarily involves its partial μ-agonist activity. Dezocine has demonstrated morphine-like properties in comparative analgesic studies in human volunteers. When administered to subjects who had previously received morphine, dezocine increased the level of analgesia[26] (Fig. 2). This effect may be attributed to the agent's δ-agonist and minimal κ-agonist activity.[26] However, dezocine, unlike pentazocine, butorphanol, and nalbuphine, is primarily a μ-agonist.[60]

When binding sites were examined in rat brain tissue, dezocine was found to have a tenfold greater affinity for μ-receptors than for δ-receptors (which may modify a μ-response) and a 40-fold greater affinity for μ- than for κ-receptors.[60] Although there has been one report of dysphoria occurring after high doses of dezocine in a human,[70] the drug has little affinity for the σ-receptor. Other agonist-antagonist agents, such as nalorphine, nalbuphine, butorphanol, and pentazocine, have more psychomimetic effects, presumably because of their σ-receptor actions.[26, 39] The dependence liability of dezocine is considered to be minimal.[87] Currently, dezocine, nalbuphine, and butorphanol are the only agonist-antagonists commonly in use that are not controlled substances in the United States. Pentazocine is a controlled class IV drug, whereas buprenorphine is a controlled class V agent.

There is some controversy about the abuse potential of dezocine. After long-term administration of dezocine to rhesus monkeys, none

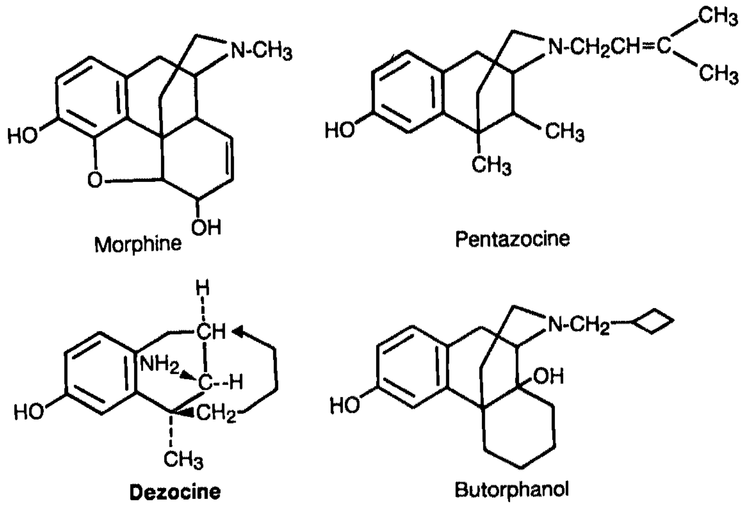


Figure 1. Structure of dezocine, pentazocine, butorphanol, and morphine. (*From* O'Brien JJ, Benfield P: Dezocine: A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs 38:226–248, 1989; with permission.)

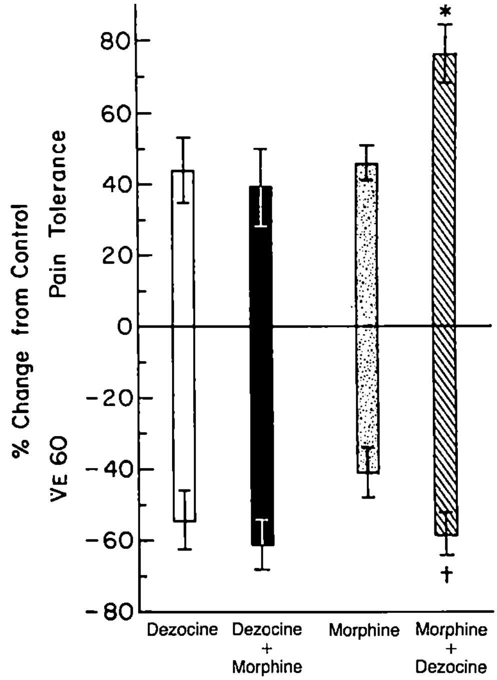


Figure 2. Changes in tolerance to experimental pain and ventilation after 0.15 mg/kg doses of dezocine and morphine given alone and in combination. Values are mean ± SEM for six subjects expressed as the percent change from control. V_E60 denotes minute ventilation at P_{CO_2} equal to 60 mm Hg during rebreathing. The asterisk denotes a value significantly different from those achieved with all other treatments ($P < 0.01$). The + denotes a value significantly different from that obtained with morphine ($P < 0.05$). (*From* Gal TJ, DiFazio CA: Ventilatory and analgesic effects of dezocine in humans. Anesthesiology 61:716–722, 1984; with permission.)

of the animals had signs of withdrawal, either on abrupt cessation of dezocine or administration of nalorphine. In contrast, in similar studies of long-term administration of morphine and pentazocine, monkeys had withdrawal symptoms. Dezocine did precipitate withdrawal symptoms when administered to morphine-dependent rhesus monkeys, with the symptoms being similar to those produced by nalorphine in morphine-dependent monkeys.[53]

The ability of dezocine to cause withdrawal symptoms in morphine-dependent humans has not been studied. However, Jasinski and Preston[42] investigated the relative abuse potential of dezocine in 10 nondependent drug abusers who were asked to compare the effects of subcutaneous doses of morphine (15 and 30 mg), dezocine (15, 30, and 60 mg), and a placebo. They found that morphine and dezocine were equally potent and, in comparison with the placebo, caused pupillary miosis, increased liking, and euphoria. Subjects consistently identified both agents as "dope."[42] These findings contrast with those of studies of other agonist-antagonists, primarily κ-agonist agents such as pentazocine, which drug abusers do not readily identify as opioids.[42] Although Jasinski and Preston concluded that dezocine may be abused, they also maintained that because the drug's effect reaches a plateau level with increasing dosage and studies in animals have shown no physical-dependence tendencies, dezocine has much less abuse potential than traditional morphine μ-type agents.

The World Health Organization Expert Committee on Drug Dependence has recommended against scheduling dezocine as a controlled substance.[87] Further investigation is required to determine whether the drug can precipitate withdrawal symptoms in morphine-dependent humans and whether it has substantial dependence and abuse liabilities.

Pharmacokinetics

The only study of the pharmacokinetics of dezocine in human volunteers revealed that serum concentration time curves from single intravenous (IV) doses (5, 10, and 20 mg) were biphasic in nature, displaying a rapid initial distribution followed by a slow terminal elimination (Table 1).[48] Dezocine has a large volume of distribution, indicating extensive extravascular or tissue uptake. Elimination occurs through a combination of renal excretion of the intact drug and metabolism, primarily in the liver. When given as an IV bolus dose, dezocine has a short half-life of 2.4 to 2.7 hours and a rapid clearance. This suggests the existence of other mechanisms of clearance, such as biliary excretion.

Analgesic Activity

The analgesic effect of dezocine is nearly equal to that of morphine and five to nine times that of meperidine. In a study of analgesic properties, dezocine was found to be comparable to morphine in altering volunteers' response to tourniquet-induced ischemic pain.[26] Interestingly, the analgesic effect of dezocine reached a plateau at a dose of 0.3 mg/kg; higher doses did not further augment pain tolerance (Fig. 3). The analgesic effects of dezocine have been quickly reversed by naloxone in both laboratory and clinical studies.[53, 81]

Table 1. PHARMACOKINETIC VARIABLES AFTER SINGLE DOSES OF DEZOCINE IN HEALTHY MEN

No. of Subjects	Route	Dose (mg)	T½ (h)	VD (L/kg)	CL_S (L/h/kg)
12	IV	5	2.6	12	3.1
		10	2.4–2.7	11	3.0
		20	2.8	9*	2.5*
24	IM	10	2.2		
	SC	10	2.5		

Abbreviations: T½ = mean elimination half-life; VD = volume of distribution; CL_S = total body clearance; IV = intravenous; IM = intramuscular; SC = subcutaneous.

*Values significantly different from those for 5- and 10-mg doses ($P < 0.05$).

From Locniskar A, Greenblatt DJ, Zinny MA: Pharmacokinetics of dezocine, a new analgesic: Effect of dose and route of administration. Eur J Clin Pharmacol 30:121–123, 1986; with permission.

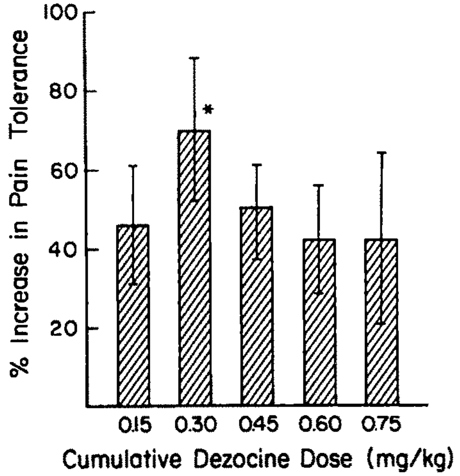


Figure 3. Altered responses to experimental pain after each of five successive 0.15 mg/kg doses of dezocine. Values are mean ± SEM for six subjects, expressed as percent change from control. The asterisk denotes a value significantly greater than that observed with previous dose ($P < 0.05$). (*From* Gal TJ, DiFazio CA: Ventilatory and analgesic effects of dezocine in humans. Anesthesiology 61:716–722, 1984; with permission.)

Respiratory Effects

Studies in healthy volunteers have demonstrated that the respiratory depression associated with increasing doses of dezocine reaches a plateau (ceiling) level.[26, 70] The effects of other agonist-antagonists, such as nalbuphine, also attain a respiratory-depression plateau with increasing doses.[18] Purely μ-receptor opioid agonists, such as morphine, do not show such a ceiling effect with increasing doses.[26, 70]

Two studies compared the effects on respiration of single doses of morphine and dezocine. Romagnoli and Keats[70] found that the effects of dezocine (10 mg/70 kg) had a more rapid onset (10 versus 24 minutes) and that the drug created more displacement of the carbon dioxide response curve (8.1 versus 5.8 mm Hg $PaCO_2$) when compared with the same dose of morphine. They also observed a plateau with respect to respiratory depression at doses of dezocine higher than 30 mg/70 kg, whereas the same doses of morphine continued to displace the carbon dioxide response curve (Fig. 4).[70]

Gal and DiFazio[26] studied the ventilatory effects of dezocine and morphine in subjects on mouth-occlusion pressure at 60 mm Hg CO_2 and minute ventilation. They found that 0.15 mg/kg of dezocine caused more respiratory depression during the first hour after administration than the same dose of morphine. They also determined that a ceiling effect with respect to respiratory depression and analgesia occurred with doses of dezocine higher than 0.3 mg/kg.[26]

When 0.15 mg/kg of dezocine was administered intravenously and followed by 0.15 mg/kg of morphine, the respiratory and analgesic effects observed were similar to those occurring with dezocine alone. In contrast, when 0.15 mg/kg of morphine was followed by 0.15 mg/kg of dezocine, the results were markedly different. The respiratory depression was identical to that occurring with the initial sequence of administration, but the analgesic effects were significantly greater than

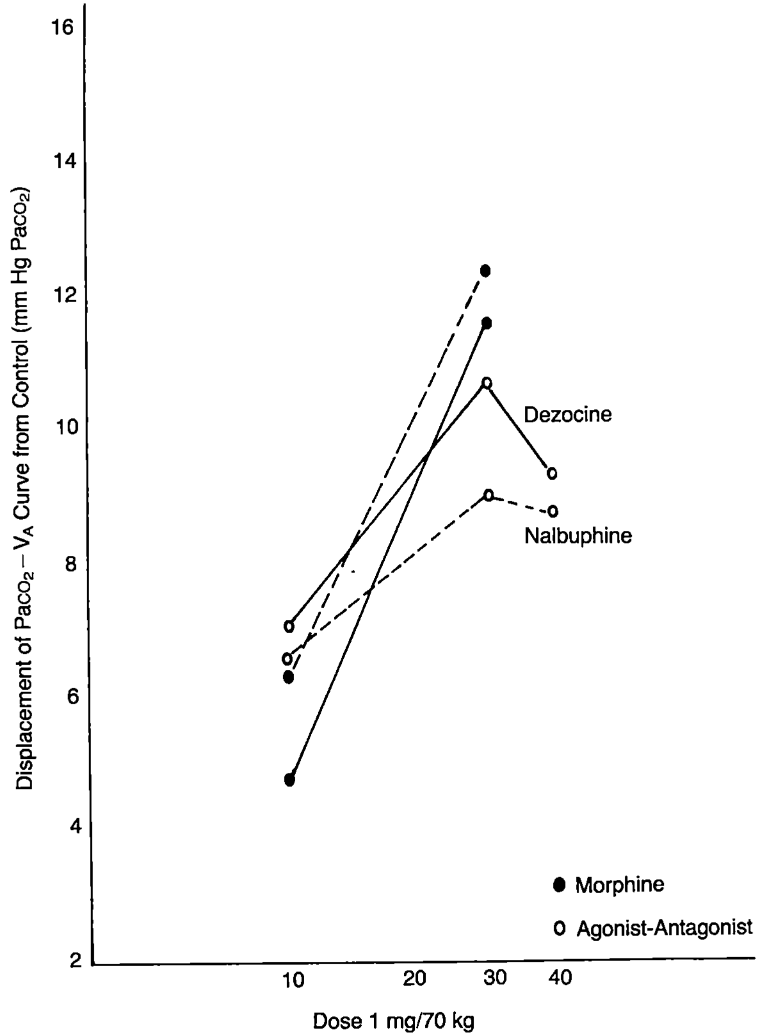


Figure 4. Calculated dose-effect curves for respiratory depression by cumulative doses of morphine, dezocine, and nalbuphine. Slopes of the agonist-antagonist curves were significantly less than the morphine curves. (*From* Romagnoli A, Keats AS: Ceiling respiratory depression by dezocine. Clin Pharmacol Ther 35:367–373, 1984; with permission.)

those achieved with dezocine given alone or first.[26] These results are somewhat contradictory to what might be expected, because the finding that dezocine has antagonist properties in monkeys indicates that it should decrease analgesia and respiratory depression when administered after morphine in humans.

The observation that dezocine increases analgesia when given after morphine has three possible explanations. First, dezocine may have more affinity at the μ-receptor than does morphine. Second, the action of morphine at the μ-receptor may be enhanced by the action of dezocine on the δ-receptor, which can influence the μ-receptor. Finally, the action of dezocine at the κ-receptor, though minimal, may increase morphine analgesia when morphine is given first.[26]

Cardiovascular Effects

In studies in animals, the principal hemodynamic effect of dezocine has been dose-related hypotension. When dogs were given an IV bolus of 20 mg/kg of dezocine with 1% enflurane, there was no change in heart rate, a 61% decrease in mean arterial pressure, a 40% reduction in cardiac output, and a 31% decrease in stroke volume. There were no significant differences in hemodynamics in dogs receiving a bolus of up to 5 mg/kg and control dogs. When dezocine was given as a bolus of 80 mg/kg, severe myocardial depression developed, with no change in systemic vascular resistance and filling pressures.[35]

Lewis and Kirchner[47] found that a bolus dose of 8 mg/kg of dezocine in dogs did not affect heart rate, but did cause hypotension. When dezocine was given as a bolus of 2 mg/kg or when 8 mg/kg was infused over 2 minutes, blood pressure did not change. In addition, a bolus dose of 8 mg/kg did not increase plasma histamine levels.[47]

The hemodynamic effects of dezocine in humans have been studied only in patients undergoing cardiac catheterization. At a dose of 0.125 mg/kg (10 mg in an 80-kg person), dezocine caused a significant increase in cardiac index, stroke volume, and left ventricular stroke-work index and a significant decrease in systemic vascular resistance from baseline values. Dezocine caused no significant changes in heart rate, mean arterial pressure, and pulmonary capillary wedge pressure. There was a transient increase in mean pulmonary artery pressure and pulmonary vascular resistance.[74] Although dezocine produced only minimal hemodynamic changes in subjects undergoing cardiac catheterization, the drug should be used with caution in patients with myocardial dysfunction or ischemia until additional hemodynamic studies are conducted.

Clinical Trials

It is not easy to judge the efficacy and relative potencies of analgesic drugs. A drug's apparent effects may vary greatly among patients because of the subjective nature of pain and the difficulty in quantifying the pharmacodynamic effects of opioids and any placebo response. In recent studies of fentanyl and sufentanil, electroencephalography was used to measure opioid pharmacodynamics.[76] Therapeutic trials with dezocine have used verbal and analogue pain scales or a 50% pain-relief scale.[60]

Several placebo- and nonplacebo-controlled comparative studies have evaluated the efficacy of dezocine. Downing et al[19] found that

10 mg of intramuscular (IM) dezocine had the same analgesic properties as 10 mg of morphine, when given for postoperative pain (Fig. 5). They also determined that the drugs had the same onset time and a similar duration of action. When the dose of IM dezocine was increased to 15 mg, it provided better analgesia than 10 mg of morphine.[19]

In a double-blind, placebo-controlled investigation of IV dezocine and morphine, the analgesics provided significantly better postoperative pain relief than placebo. In comparisons of the two drugs, both physicians and patients gave dezocine a higher overall analgesia rating.[65]

Two studies have compared IM dezocine with IM meperidine for

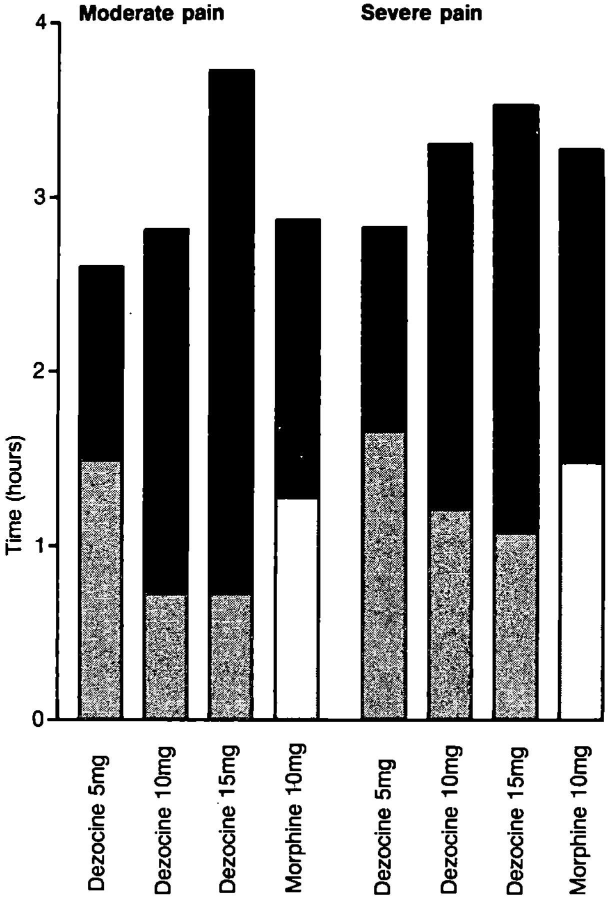


Figure 5. Mean latency of onset (*light gray and dark gray*) and duration (*black*) of effective pain relief (≥ 50% on a six-point verbal scale) after single intramuscular doses of dezocine and morphine in 160 patients with moderate to severe pain. (*Data from* Downing JW, Brock-Utne JG, Barclay A, et al: Wy 16225 (dezocine), a new synthetic opiate agonist-antagonist and potent analgesic: A comparison with morphine for relief of pain after lower abdominal surgery. Br J Anaesth 53:59–64, 1981; and *modified from* O'Brien JJ, Benfield P: Dezocine: A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs 38:226–248, 1989; with permission.)

postoperative analgesia. A dose of 100 mg of meperidine was more effective than 10 mg of dezocine but not as effective as 15 mg of dezocine.[13] When compared with 50 mg of meperidine, 10 mg of dezocine was judged to be equally effective.[24] Both studies determined that dezocine was five to nine times as potent as meperidine.

Two placebo-controlled, double-blind studies have compared dezocine with butorphanol for postoperative pain.[21, 27] Both analgesics were found to be superior to placebo, and 10 mg of IM dezocine was considered to provide the same or better analgesia than 2 mg of butorphanol.

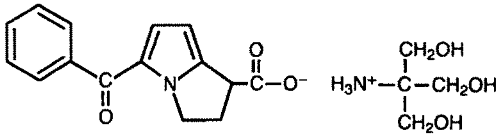
The most common adverse effects of dezocine are nausea, vomiting, somnolence, and prolonged sedation. The sedation produced by 10 to 15 mg of IM dezocine has a peak effect similar to that of morphine but of shorter duration; it is maximal about 1 hour after the dose is administered.[64] There have been isolated reports of respiratory depression (with 15 mg of IM dezocine) and hypotension.[65, 81] The hypotension responded to supportive measures,[65] and the respiratory depression was reversed by naxolone.[81] Naloxone should easily reverse any respiratory depression due to dezocine because of the ceiling effect associated with the analgesic and the fact that it does not bind as tightly to the μ-receptor as does buprenorphine. No overdoses of dezocine have been reported.

Additional clinical studies of dezocine are needed. No investigations of its use during general anesthesia (including its respiratory and hemodynamic effects in anesthetized patients) have been conducted. The use of spinal dezocine has been studied in dogs.[16] Unfortunately, leptomeningeal reactions occurred after long-term administration; additional examinations of this phenomenon are needed. Other areas of investigation include the effect of dezocine on biliary pressure and histamine release, the use of dezocine to treat pruritus due to spinal opiates and to reverse opiate-induced respiratory depression, and the potential role of high-dose dezocine in cardiac anesthesia.

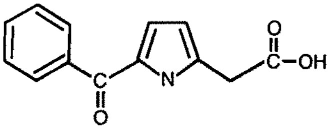
KETOROLAC

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs; its chemical name is (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2a]pyrrole-1-carboxylic acid. The drug, which is structurally related to tolmetin and zomepirac (Fig. 6), has anti-inflammatory, antipyretic, and pronounced analgesic activity. In studies in animals, ketorolac has been found to be a more potent analgesic than aspirin, phenylbutazone, naproxen, or indomethacin.[71, 72]

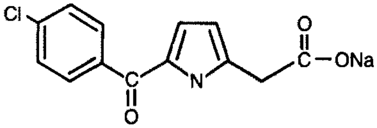
Ketorolac's mechanism of action as an analgesic has not yet been described. The agent does prevent prostaglandin synthesis by inhibiting cyclooxygenase, the principal enzyme that catalyzes the reaction with arachidonic acid to form prostaglandins (Fig. 7).[12, 71, 72] No evidence suggests that ketorolac has any opiate properties, because it does not



Ketorolac



Tolmetin



Zomepirac

Figure 6. Structure of ketorolac, tolmetin, and zomepirac. (*From* Buckley MM-T, Brogden RN: Ketorolac: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 39:86–109, 1990; with permission.)

bind to μ-, κ-, or δ-receptors and, when used on a long-term basis and then stopped, it does not produce any of the withdrawal symptoms occurring with opioids.[49, 93]

Because ketorolac does not bind to opiate receptors, it has no abuse potential, does not promote drug dependence, and will not precipitate withdrawal symptoms if it is suddenly discontinued after long-term administration.[93]

Pharmacokinetics

In the United States, ketorolac is currently (1991) approved only for IM use, although the IV formulation is being evaluated by the Food

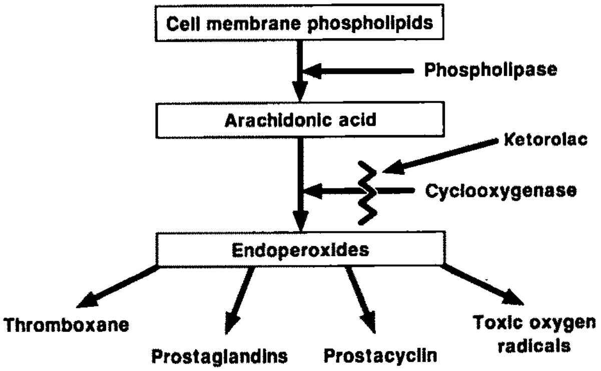


Figure 7. Site of action of ketorolac. (© 1990, Syntex Laboratories, Inc.; with permission.)

and Drug Administration. The pharmacokinetics of a 30-mg IM dose have been studied in both young and elderly volunteers, as well as in patients with hepatic or renal dysfunction (Table 2).[12] The plasma maximum concentration after an IM dose is reached in 45 to 50 minutes. The drug is highly protein bound[59] and has a small volume of distribution (0.17–0.25 L/kg).[44, 59] The terminal elimination half-life in healthy volunteers is 4.5 hours. In elderly patients,[56] patients with hepatic dysfunction,[63] and those with renal dysfunction,[54] the terminal elimination half-life values are 7.0, 5.4, and 9.6 hours, respectively. The plasma clearance of ketorolac ranges from 0.027 L/h/kg in young volunteers to 0.016 L/h/kg in patients with renal dysfunction. The principal metabolic pathway of ketorolac is through glucuronic acid conjugation. Its major route of elimination is urinary excretion; up to 90% of an administered dose may be recovered in the urine.[59]

The pharmacokinetics of IM ketorolac are apparently most altered in elderly patients[56] and those with renal failure.[54] As a result, the loading and maintenance doses given to them must be reduced appropriately. Studies in patients with hepatic dysfunction have found that any alterations in the pharmacokinetics of ketorolac in this group were minimal and had no clinical importance.

In pregnant patients, the ratio of fetal-to-maternal plasma concentrations of ketorolac is lower than that of opioid analgesics.[84] Ketorolac is not recommended for obstetric analgesia because of the known effects of other drugs that inhibit prostaglandin synthesis on the fetal cardiovascular system (closure of the ductus arteriosis) and on uterine contraction.

In a study in lactating women, a 10-mg oral dose of ketorolac produced a breast-milk concentration of 7.3 ng/mL.[89] Ketorolac should be used with extreme caution in nursing mothers because of its possible adverse effects on the cardiovascular system of neonates.

Table 2. THE INFLUENCE OF AGE AND LIVER AND KIDNEY FUNCTION ON THE CLEARANCE AND TERMINAL HALF-LIFE OF KETOROLAC*

Subject Group	Total Clearance (L/h/kg)†	Terminal Half-Life (h)†
Normal subjects (n = 8)	0.026 (0.017–0.046)	4.5 (3.8–5.0)
Patients with hepatic dysfunction (n = 7)	0.029 (0.013–0.066)	5.4 (2.2–6.9)
Patients with renal impairment (n = 10)	0.016 (0.007–0.043)	9.6 (3.2–5.7)
Healthy elderly subjects (n = 13)	0.019 (0.013–0.034)	7.0 (4.7–8.6)

*Estimated from 30-mg single doses of ketorolac.
†Values are mean (range).
© 1990, Syntex Laboratories, Inc.; with permission.

Respiratory and Cardiovascular Effects

When compared with morphine, 10 to 90 mg of IM ketorolac had virtually no effect on end-tidal P_{CO_2} and the carbon dioxide response curve in volunteers breathing carbon dioxide (Fig. 8).[8] A minimal increase in arterial P_{CO_2} was observed when ketorolac was infused intramuscularly at a rate of 1.5 to 3.0 mg/h.[32] In a study comparing IV doses of 10 to 90 mg of ketorolac with IV morphine in anesthetized patients, ketorolac had no effect on mean arterial pressure, cardiac output, or systemic vascular resistance.[14]

Clinical Trials

As with dezocine, the analgesic effects of ketorolac are difficult to measure because of the subjective nature of pain. Furthermore, there

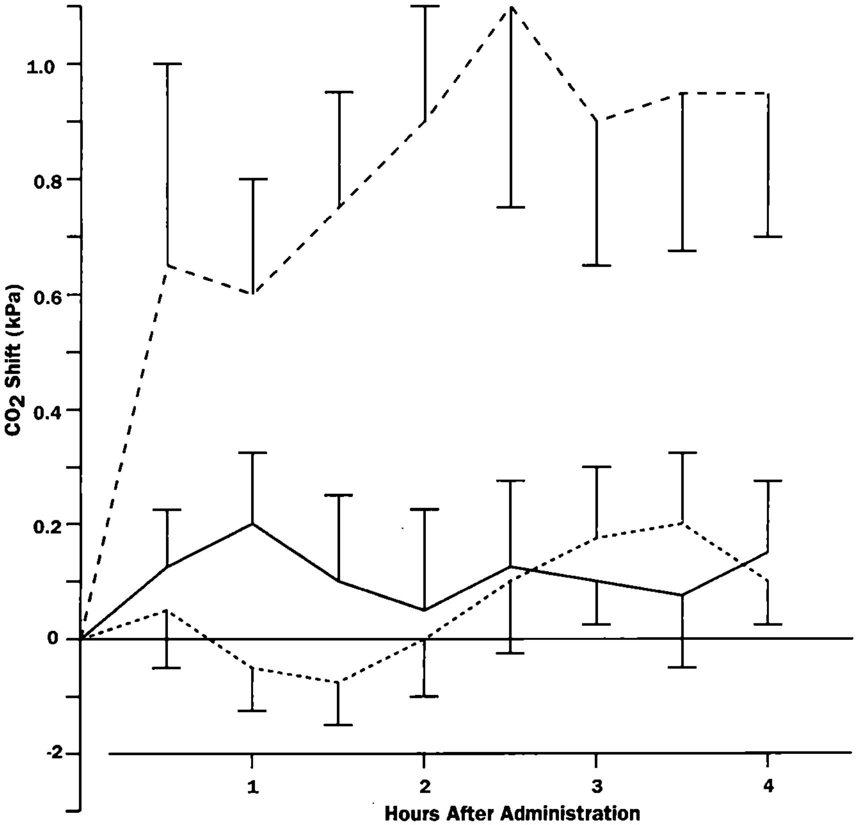


Figure 8. Mean carbon dioxide shift. Time profiles following administration of single doses of 10 mg (*solid line*) or 90 mg (*small-dashed line*) of ketorolac, or 10 mg of morphine (*large-dashed line*) to nine healthy volunteers (error bars represent 1 SD). (*From* Brandon Bravo LJC, Mattie H, Spierdijk J, et al: The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 35:491–494, 1988; with permission.)

have been few clinical trials of ketorolac by independent investigators. No intraoperative studies have determined whether, when, and how much ketorolac affects the minimum alveolar concentration of inhalation agents.

In a placebo-controlled study, IM ketorolac infused at 1.5 and 3.0 mg/h provided significantly better analgesia after upper abdominal surgery than a saline infusion.[32] Ketorolac also decreased the morphine requirement for postoperative pain by one third in comparison with placebo.[32] In clinical trials comparing IM morphine with ketorolac, 30 mg of ketorolac was found to be as effective as 12 mg of morphine against moderate postoperative pain.[61, 92] Figure 9 shows that 30 mg of ketorolac is equivalent to 90 mg of ketorolac in treating moderate pain. For severe postoperative pain, 90 mg of ketorolac is superior to 100 mg of meperidine[25, 91] and 12 mg of morphine.[61, 92] Unfortunately, the 90-mg dosage regimen of ketorolac can cause gastric irritation when used on a long-term basis.[46]

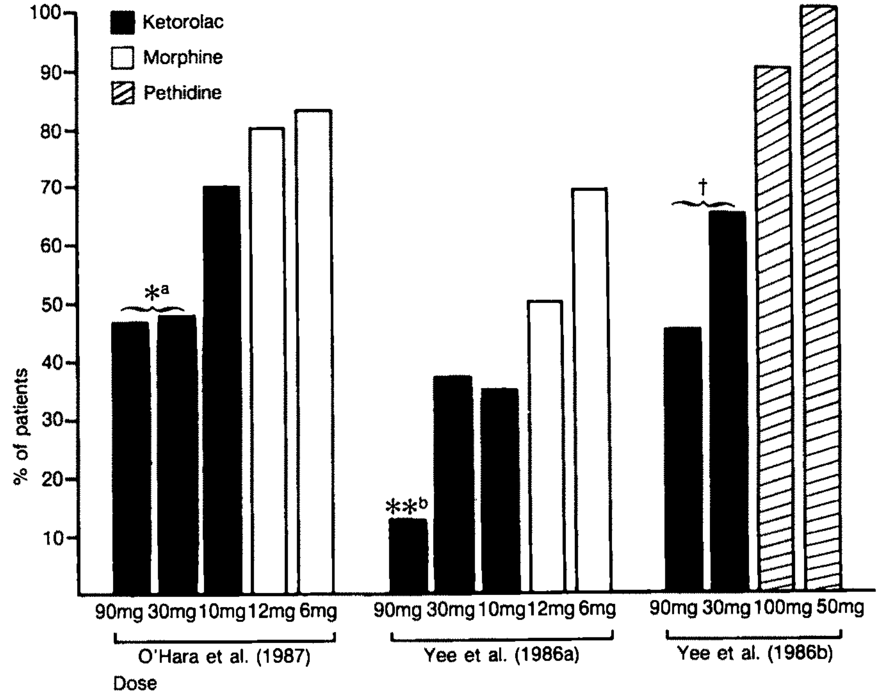


Figure 9. Percentage of patients requiring remedication or terminating study because of inadequate pain relief in studies comparing IM ketorolac with opioid agents for postoperative pain for up to 6 hours; *[a] denotes ketorolac significantly better than 12 and 6 mg of morphine ($P < 0.05$); **[b] denotes 90 mg of ketorolac significantly better than 30 or 10 mg of ketorolac and 12 mg of morphine ($P < 0.005$). The † denotes ketorolac significantly superior (*P* value not stated). (*From* Buckley MM-T, Brogden RN: Ketorolac: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 39:86–109, 1990; with permission.)

In doses of 30 to 60 mg, ketorolac will provide up to 6 hours of analgesia, whereas the equivalent doses of morphine will provide only 3 to 4.[12] The dosage regimen for IM ketorolac includes a loading dose of 30 to 60 mg, followed by a maintenance dose of 15 to 30 mg every 6 hours.[12]

Only one study has compared IV morphine with IV ketorolac for postoperative analgesia.[10] Evaluation of pain scores obtained 1 hour after administration suggested that 10 mg of ketorolac was superior to 4 mg of morphine. Ketorolac also has been shown to be effective against pain due to trauma, renal colic, and cancer.[12]

Adverse Effects

Studies have found no significant differences between morphine and ketorolac with respect to the type of side effects they produce and the rates at which such effects occur.[61, 92] The most common adverse effects of ketorolac are somnolence, nausea, vomiting, dry mouth, sweating, and palpitations. Minimal pain on injection has been reported. An investigation of the long-term use of parenteral ketorolac found that the incidence of gastric and duodenal mucosal erosions resulting from 90-mg IM doses given four times a day was comparable with that occurring with 650 mg of aspirin given orally four times a day.[46] The investigators suggested that parenteral doses of ketorolac be limited to 30 mg or less.

When given on a long-term basis, ketorolac, like other nonsteroidal anti-inflammatory drugs, increases bleeding time.[15] It does not affect platelet count, prothrombin time, or partial thromboplastin time.

Ketorolac appears to have a role as an analgesic, but more clinical studies are required. Its advantages are that it has no dependence liabilities and minimal cardiovascular and respiratory effects. Ketorolac's structural similarities to zomepirac and tolmetin suggest that anaphylactoid reactions to it are possible, but there have been no reports of this complication.[12] The side effects of ketorolac are similar to those of other nonsteroidal anti-inflammatory drugs.

Additional studies are needed to determine the preoperative and intraoperative uses of ketorolac. Would it be a good premedication? Does it lower minimum alveolar concentration? What part might it play in anesthesia in ambulatory surgery settings and as a supplement to spinal opiates? These are a few of the questions that must be answered in order to evaluate the future of ketorolac.

α_2-AGONISTS

The use of α_2-adrenergic agonists in the perioperative period represents a new, exciting area of research in anesthesia. Miller et al[55] were the first to report that these drugs have antinociceptive properties when they found that α-methyldopa reduced minimum alveolar concentration requirements in rats. At the time their paper was published, it was believed that a metabolic product of α-methyldopa, methylnorepinephrine, acted as a false transmitter that displaced norepinephrine from both central and peripheral binding sites. It was postulated that the resulting decrease in norepinephrine reduced the concentration of inhalational anesthetic necessary to produce adequate anesthesia for surgery and to lower blood pressure. Subsequently, the false-transmitter theory was shown to be incorrect, and methylnorepinephrine was found to work by stimulating central α_2-adrenergic receptors and producing sedation, a decrease in minimum alveolar concentration, and an antihypertensive effect.[5, 69]

The exact mechanism by which α_2-agonists reduce anesthetic requirements and produce analgesia remains unknown. They probably activate presynaptic and postsynaptic receptors at noradrenergic pathways involved in endogenous pain control in the dorsal horn of the spinal cord and at supraspinal levels.

Clonidine

Most current research on α_2-agonists has focused on clonidine and dexmedetomidine, which are more specific α_2-agonists than α-methyldopa. Clonidine was first shown to produce analgesia when administered systemically to mice and rats.[62] In mice, clonidine enhances morphine analgesia without affecting the morphine-specific μ-receptor.[78] Clonidine also has been found to decrease the intraoperative anesthetic requirements for both opioids and volatile agents and to prevent large hemodynamic fluctuations.[23, 30, 31]

Perioperatively, clonidine can be administered parenterally,[3, 6, 34] orally,[23] intrathecally,[7, 68] epidurally,[20, 58] and by transdermal patch.[76] Although many studies have attested to the efficacy of clonidine[23, 30, 31] and dexmedetomidine[1] as adjuncts in anesthesia and when used intrathecally[7, 68] and epidurally[6, 20] for postoperative analgesia, few investigations have examined their analgesic effects when administered systemically.[3, 6, 34]

Epidural clonidine by itself does not appear to provide complete pain relief after major surgery unless more than 300 μg is given; unfortunately, sedation, hypotension, and bradycardia commonly occur at such doses.[20] Patients undergoing thoracotomy who received 3 μg/kg of epidural clonidine did not have adequate postoperative analgesia in a placebo-controlled trial.[33] In another study, however, 2 μg/kg of epidural clonidine provided analgesia for a mean of 3.5 hours in patients undergoing perineal or orthopedic surgery.[6] Epidural clonidine will probably be most useful as an adjunct to epidural opioids. One study found that, when the agent was infused at approximately 20 μg/h, it enhanced the analgesia produced by epidural morphine in patients having major abdominal surgery.[58]

Only a few studies of the use of systemic clonidine as an analgesic agent have been conducted. In one, oral clonidine (150–300 μg) did not prolong analgesia from spinal blockade when compared with subarachnoid clonidine.[7] Case reports have described the analgesic affects of systemic clonidine in patients with diffuse musculoskeletal pain[79] and carcinoma.[67] One study comparing epidural clonidine (2 μg/kg) and the same dose of IM clonidine found that the IM formulation provided adequate analgesia for up to 3 hours when given to patients fully recovered from an epidural lidocaine sensory block for orthopedic or perineal surgery.[6]

Two studies have examined the postoperative analgesic effects of IV clonidine. In the first, a comparison with placebo and 50 mg of IV meperidine showed that 100 μg of IV clonidine provided less analgesia than placebo, whereas 200 μg of IV clonidine provided the same pain relief as 50 mg of meperidine.[34] In the second study, a 5 μg/kg loading dose of IV clonidine followed by a 0.3 μg/kg/h infusion markedly decreased postoperative morphine requirements in patients who had undergone posterior spine fusions.[3]

Clonidine has also been used in an oral-transdermal formulation to treat perioperative pain.[77] In a placebo-controlled study, patients were given 3 to 4.5 μg/kg of oral clonidine the night before surgery, 3 to 6 μg/kg the morning of surgery, and a 7- to 10.5-cm^2 transdermal patch postoperatively. All those who received clonidine had more preoperative sedation and required less morphine postoperatively. Plasma concentrations of clonidine in the perioperative period were 1.32 to 1.93 ng/mL, a finding that correlates well with those of many other studies with respect to the optimal plasma concentration of the drug required to produce sedation, an antihypertensive effect, and dry mouth.

Hemodynamic and Respiratory Effects

Clonidine has two principal effects on the cardiovascular system; both are dose dependent. At low plasma levels (1.5–2.0 ng/mL), the drug produces central hypotension and bradycardia. Cardiac output may decrease slightly or remain unchanged because of the bradycardia and decreased afterload and preload.[9, 17, 52, 88] At plasma levels of 4 ng/mL, patients become normotensive,[52, 88] but at levels higher than 10 ng/mL, transient hypertension occurs as a result of the drug's direct effects on vascular smooth muscle.[88]

There is some controversy about the respiratory effects of clonidine. Some researchers have suggested that it has minimal respiratory effects,[23] but preliminary reports have found an increased rate of ventilatory depression.[66, 75, 80] In a recent study in healthy volunteers, 0.3 to 0.4 mg of oral clonidine did not decrease the ventilatory response to carbon dioxide. Furthermore, when clonidine was added to a morphine regimen, the ventilatory response to carbon dioxide was not significantly different than that observed with morphine alone.[2] It appears that clonidine produces little respiratory depression in healthy adults.

In elderly patients with cardiopulmonary disease, however, its effects may be quite different.

Pharmacokinetics

After an oral dose of 300 μg of clonidine, plasma levels of the drug reach a peak in 1 to 2 hours.[50] The plasma levels are characterized by rapid distribution followed by a β-elimination half-life of 5 to 13 hours. After IV administration, there is a large volume of distribution (2 L/kg) because of the high lipid solubility of the drug. About 20% to 40% is bound to plasma protein. Clonidine is cleared primarily by renal excretion.[50]

Dexmedetomidine

Dexmedetomidine, a stereoisomer of medetomidine, is a more highly selective α_2-agonist than clonidine.[82] Two placebo-controlled studies have investigated dexmedetomidine as an adjunct in anesthesia and examined its effects on pain. When patients were given 0.5 μg/kg of IV dexmedetomidine before minor gynecologic surgery, they required less thiopental and had lower plasma norepinephrine levels than matched controls. Blood pressure was lower in the dexmedetomidine group, but there was no difference in heart rate.[1]

In the second study, patients received 25 μg of IV dexmedetomidine that was followed by a second 25-μg dose given 15 minutes later.[45] A significant sedative effect and a decrease in blood pressure were produced, with no change in heart rate. The pain threshold to electric stimulation of the tooth pulp, cutaneous thermal pain, and tourniquet-induced pain was not changed by dexmedetomidine, although a decrease in the "unpleasantness" of the tourniquet pain was reported. Whether higher doses of dexmedetomidine would provide better analgesia and cause less hypotension in clinical pain syndromes requires further investigation.

The side effects of systemic α_2-agonists are hypotension, bradycardia, sedation, and dry mouth.[50] It is unlikely that either systemic clonidine or dexmedetomidine will ever be used alone as an analgesic. Instead, α_2-agonists will probably be employed chiefly as adjuncts to systemic opiates.

CAPSAICIN

Capsaicin, the active ingredient in Hungarian hot peppers, apparently inactivates small C-type fibers.[38] Although its mechanism of action is unclear, capsaicin depletes substance P, which mediates cutaneous pain, from peripheral nerves.[11, 28, 37, 38, 43, 90] Capsaicin can also block axonal transport,[29, 36, 51] cause damage to peripheral nerves,[22, 40] and alter action potentials.[85] In a study in which capsaicin was applied to the skin of volunteers, the subjects had changes in perception in response to pinprick, heat, and cold.[83] When a 0.025% concentration of capsaicin cream is applied cutaneously, subjects may initially complain of a burning sensation.

Currently, capsaicin cream is used topically for postherpetic neuralgia[4, 86] and for lower extremity dysesthesias due to Guillain-Barré syndrome.[57] Capsaicin may eventually have a role in localized nerve blocking because it has no effect on sympathetic A fibers. It may also be useful in patients with diabetic peripheral neuropathies.[73] Although capsaicin has not been used systemically, its oral toxicity is low; up to 20 mg is consumed in some spicy food dishes.[41] Moreover, IV injection of 2.5 mg of the agent does not produce any cardiorespiratory effects. Future investigations should focus on capsaicin's effect on tourniquet pain.

SUMMARY

The perioperative roles of dezocine, ketorolac, and α_2-agonists have not yet been completely defined, although these agents are known to have some advantages over opiate analgesics. Further investigation is needed to determine whether dezocine and ketorolac will replace or supplement opiates. α-Agonists will probably always be used as adjuncts to opiates because they are not complete analgesics. Capsaicin has not been employed systemically, but its local effects may be found to be useful in the perioperative period.

References

1. Aantaa R, Kanto J, Scheinin M, et al: Dexmedetomidine, an alpha-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology 73:230–235, 1990
2. Bailey PL, Sperry RJ, Johnson GK, et al: Respiratory effects of clonidine alone and combined with morphine in humans. Anesthesiology 74:43–48, 1991
3. Bernard JM, Lechevalier T, Pinaud M: Postoperative analgesia by intravenous clonidine [abstract]. Anesthesiology 71:A154, 1989
4. Bernstein JE, Bickers DR, Dahl MV, et al: Treatment of chronic postherpetic neuralgia with topical capsaicin. J Am Acad Dermatol 17:93–96, 1987
5. Bobik A, Jennings G, Jackman G, et al: Evidence for a predominantly central hypotensive effect of alpha-methyldopa in humans. Hypertension 8:16–23, 1986
6. Bonnet F, Boico O, Rostaing S, et al: Clonidine-induced analgesia in postoperative patients: Epidural versus intramuscular administration. Anesthesiology 72:423–427, 1990
7. Bonnet F, Catoire P, Buisson VB, et al: Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anaesth 15:211–214, 1990
8. Brandon Bravo LJC, Mattie H, Spierdijk J, et al: The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 35:491–494, 1988
9. Brest AN: Hemodynamic and cardiac effects of clonidine. J Cardiovasc Pharmacol 2:S39–S46, 1980
10. Brown CR, Wild VM, Bynum L: Comparison of intravenous ketorolac tromethamine

and morphine sulfate in postoperative pain [abstract]. Clin Pharmacol Ther 43:142, 1988

11. Buck SH, Miller MS, Burks TF: Depletion of primary afferent substance P by capsaicin and dihydrocapsaicin without altered thermal sensitivity. Brain Res 233:216–220, 1982
12. Buckley MM-T, Brogden RN: Ketorolac: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 39:86–109, 1990
13. Camu F, Gepts E: Analgesic properties of dezocine for relief of postoperative pain. Acta Anaesthesiol Belg 30(suppl):183–191, 1979
14. Camu F, Van Overberghe L, Bullingham R, et al: Hemodynamic effects of ketorolac tromethamine in comparison to morphine in anesthetised patients [abstract A0167]. *In* Proceedings of the Ninth World Congress of Anaesthesiologists, USA, 1988
15. Conrad KA, Fagan TC, Mackie MJ, et al: Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 43:542–546, 1988
16. Coombs DW, Deroo DB, Colburn RW, et al: Toxicity of chronic spinal analgesia in a canine model: Neuropathologic observations with dezocine lactate. Reg Anaesth 15:94–102, 1990
17. Davies DS, Wing LMH, Reid JL, et al: Pharmacokinetics and concentration effect relationships of intravenous and oral clonidine. Clin Pharmacol Ther 21:593–601, 1977
18. DiFazio CA, Moscicki JC, Magruder MR: Anesthetic potency of nalbuphine and interaction with morphine in rats. Anesth Analg 60:629–633, 1981
19. Downing JW, Brock-Utne JG, Barclay A, et al: Wy 16225 (dezocine), a new synthetic opiate agonist-antagonist and potent analgesic: A comparison with morphine for relief of pain after lower abdominal surgery. Br J Anaesth 53:59–64, 1981
20. Eisenach JC, Lysak SZ, Giscomi CM: Epidural clonidine analgesia following surgery: Phase 1. Anesthesiology 71:640–646, 1989
21. Finucane BT, Floyd JB, Petro DJ: Postoperative pain relief: A double-blind comparison of dezocine, butorphanol, and placebo. South Med J 79:548–552, 1986
22. Fitzgerald M: Capsaicin and sensory neurones—A review. Pain 15:109–130, 1983
23. Flacke JW, Bloor BC, Flacke WE, et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11–19, 1987
24. Fragen RJ, Caldwell N: Comparison of dezocine (Wy 16,225) and meperidine as postoperative analgesics. Anesth Analg 57:563–566, 1978
25. Fricke J, Angelocci D: The analgesic efficacy of IM ketorolac and meperidine for the control of postoperative dental pain [abstract]. Clin Pharmacol Ther 41:181, 1987
26. Gal TJ, DiFazio CA: Ventilatory and analgesic effects of dezocine in humans. Anesthesiology 61:716–722, 1984
27. Galloway FM, Varma S: Double-blind comparison of intravenous doses of dezocine, butorphanol and placebo for relief of postoperative pain. Anesth Analg 65:283–287, 1986
28. Gamse R, Holzer P, Lembeck F: Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br J Pharmacol 68:207–213, 1980
29. Gamse R, Petsche U, Lembeck F, et al: Capsaicin applied to peripheral nerves inhibits axoplasmic transport of substance P and somatostatin. Brain Res 239:447–462, 1982
30. Ghignone M, Calvillo O, Quintin L: Anesthesia and hypertension: The effect of clonidine on preoperative hemodynamics and isoflurane requirements. Anesthesiology 67:3–10, 1987
31. Ghignone M, Quintin L, Duke PC, et al: Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 64:36–42, 1986
32. Gillies GWA, Kenny GNC, Bullingham RES, et al: The morphine sparing effect of ketorolac tromethamine. Anaesthesia 42:727–731, 1987
33. Gordh Jr T: Epidural clonidine for treatment of postoperative pain after thoracotomy: A double-blind placebo-controlled study. Acta Anaesthesiol Scand 32:702–709, 1988
34. Gordh TE, Tamsen A: A study on the analgesic effect of clonidine in man. Acta Anaesthesiol Scand 27(suppl 78):72, 1983
35. Hall RI, Murphy MR, Szlam F, et al: Dezocine—MAC reduction and evidence for

myocardial depression in the presence of enflurane. Anesth Analg 66:1169–1174, 1987

36. Harner A, Keen D: Synthesis and central and peripheral axonal transport of substance P in a dorsal root ganglion-nerve preparation in vitro. Brain Res 231:379–385, 1982
37. Hayes AG, Tyers MG: Capsaicin depletes substance P from dorsal horn and skin and discriminates heat from chemical and pressure nociceptive stimuli in the conscious rat. J Physiol (Lond) 300:25, 1980
38. Holzer P, Jurma I, Gamse R, et al: Nociceptive threshold after neonatal capsaicin treatment. Eur J Pharmacol 58:511–514, 1979
39. Houde RW: Analgesic effectiveness of the narcotic agonist-antagonists. Br J Clin Pharmacol 7:2975–3085, 1979
40. Jancso G, Kiraly E, Jancso-Gabor A: Pharmacologically induced selective degeneration of chemosensitive primary sensory neurons. Nature 270:741–743, 1977
41. Jancso G, Lynn B: Possible use of capsaicin in pain therapy. Clin J Pain 3:123–126, 1987
42. Jasinski DR, Preston KL: Assessment of dezocine for morphine-like subjective effects and miosis. Clin Pharmacol Ther 38:544–548, 1985
43. Jessell TM, Iverson LL, Cuello AC: Capsaicin-induced depletion of substance P from primary sensory neurons. Brain Res 152:183–185, 1978
44. Jung D, Mroszcak E, Bynum L: Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol 35:423–425, 1988
45. Kauppila T, Kemppainen P, Tanila H, et al: Effect of systemic medetomidine, an alpha$_2$ adrenoceptor agonist, on experimental pain in humans. Anesthesiology 74:3–8, 1991
46. Lanza FL, Karlin DA, Yee JP: A double-blind placebo controlled endoscopic study comparing the mucosal injury seen with an orally and parenterally administered new nonsteroidal analgesic, ketorolac tromethamine, at therapeutic and subtherapeutic doses [abstract]. Am J Gastroenterol 82:939, 1987
47. Lewis AJ, Kirchner T: A comparison of the cardiorespiratory effects of cinamadol, dezocine, morphine and pentazocine in the anaesthetised dog. Arch Int Pharmacodyn Ther 250:73–83, 1981
48. Locniskar A, Greenblatt DJ, Zinny MA: Pharmacokinetics of dezocine, a new analgesic: Effect of dose and route of administration. Eur J Clin Pharmacol 30:121–123, 1986
49. Lopez M, Waterbury LD, Michel A, et al: Lack of addictive potential of ketorolac tromethamine [abstract]. Pharmacologist 29:136, 1987
50. Lowenthal DT, Matzek KM, MacGregor TR: Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 14:287–310, 1988
51. MacLean DB, Lewis SF: Axoplasmic transport of somatostatin and substance P in the vagus nerve of the rat, cat and guinea pig. Brain Res 307:135–145, 1984
52. Magorien RD, Hermiller JB, Unverferth DV, et al: Regional hemodynamic effects of clonidine in congestive heart failure. J Cardiovasc Pharmacol 7:91–96, 1985
53. Malis JL, Rosenthale ME, Gluckman MI: Animal pharmacology of Wy-16,225, a new analgesic agent. J Pharmacol Exp Ther 194:488–498, 1975
54. Martinez JJ, Garg DC, Pages LJ, et al: Single dose pharmacokinetics of ketorolac in healthy young and renal impaired subjects [abstract]. J Clin Pharmacol 27:722, 1987
55. Miller RD, Way WL, Eger II EI: The effects of alpha-methyldopa, reserpine, guanethidine, and iproniazid on minimum alveolar anesthetic requirement (MAC). Anesthesiology 29:1153–1158, 1968
56. Montoya-Iraheta C, Garg DC, Jallad NS, et al: Pharmacokinetics of single dose oral and intramuscular ketorolac tromethamine in elderly vs young healthy subjects [abstract]. J Clin Pharmacol 26:545, 1986
57. Morgenlander JC, Hurwitz BJ, Massey EW: Capsaicin for the treatment of pain in Guillain-Barré syndrome. Ann Neurol 28:199, 1990
58. Motsch J, Graber E, Ludwig K: Addition of clonidine enhances postoperative analgesia from epidural morphine: A double-blind study. Anesthesiology 73:1067–1073, 1990
59. Mroszczak EJ, Lee FW, Combs D, et al: Ketorolac tromethamine absorption, distribution, metabolism, excretion, and pharmacokinetics in animals and humans. Drug Metab Dispos 15:618–626, 1987

60. O'Brien JJ, Benfield P: Dezocine: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 38:226–248, 1989
61. O'Hara DA, Fragen RJ, Kinzer M, et al: Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 41:556–561, 1987
62. Paalzow L: Analgesia produced by clonidine in mice and rats. J Pharm Pharmacol 26:361–363, 1974
63. Pages LJ, Martinez JJ, Garg DC, et al: Pharmacokinetics of ketorolac tromethamine in hepatically impaired vs young healthy subjects [abstract]. J Clin Pharmacol 27:324, 1987
64. Pandit SK, Kothary SP, Pandit UA, et al: Double-blind placebo-controlled comparison of dezocine and morphine for postoperative pain relief. Can Anaesth Soc J 32:583–591, 1985
65. Pandit UA, Kothary SP, Pandit SK: Intravenous dezocine for postoperative pain: A double-blind, placebo-controlled comparison with morphine. J Clin Pharmacol 26:275–280, 1986
66. Penon C, Ecoffey C, Cohen SE: Ventilatory effects of epidural clonidine [abstract]. Anesthesiology 71:A649, 1989
67. Petros HA, Bowen-Wright RM: Epidural and oral clonidine in domiciliary control of deafferentation pain. Lancet 1:1034, 1987
68. Racle JT, Benkhaedra A, Poy JY: Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 66:442–446, 1987
69. Reid JL: Alpha-adrenergic receptors and blood pressure control. Am J Cardiol 57:6E–12E, 1986
70. Romagnoli A, Keats AS: Ceiling respiratory depression by dezocine. Clin Pharmacol Ther 35:367–373, 1984
71. Rooks II WH, Maloney PJ, Shott LD, et al: The analgesic and anti-inflammatory profile of ketorolac and its tromethamine salt. Drugs Exp Clin Res 11:479–492, 1985
72. Rooks II WH, Tomolonis AJ, Maloney PJ, et al: The analgesic and anti-inflammatory profile of (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2a]pyrrole-1-carboxylic acid (RS-37619). Agents Actions 12:684–690, 1982
73. Ross DR, Varipapa RJ: Treatment of painful diabetic neuropathy with topical capsaicin. N Engl J Med 321:474–475, 1989
74. Rothbard RL, Schreiner BF, Yu PN: Hemodynamic and respiratory effects of dezocine. Clin Pharmacol Ther 38:84–88, 1985
75. Rouge P, Dureuil B, Loiseau A, et al: Effects of clonidine on the ventilatory response to CO_2 [abstract]. Anesthesiology 71:A1090, 1989
76. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 74:34–42, 1991
77. Segal IS, Jarvis DJ, Duncan SR, et al: Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. Anesthesiology 74:220–225, 1991
78. Spaulding TC, Fielding S, Venafro JJ, et al: Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 58:19–25, 1979
79. Uhde TW, Post RM, Siever LJ, et al: Clonidine and psychophysical pain. Lancet 2:1375, 1980
80. Veillette Y, Benhamou D, Ecoffey C: Ventilatory effects of premedication with clonidine [abstract]. Anesthesiology 71:A1091, 1989
81. Vinik HR, McFarland L, Wright D, et al: Double-blind postoperative study comparing multiple doses of dezocine (WY 16225) with morphine and placebo [abstract]. Anesthesiology 57:A189, 1982
82. Virtanen R, Savola JM, Saano V, et al: Characterization of the selectivity, specificity and potency of medetomidine as an alpha$_2$-adrenoceptor agonist. Eur J Pharmacol 150:9–14, 1988
83. Walker FO, Lewis SF: Somesthetic and electrophysiologic effects of topical 0.025% capsaicin in man. Reg Anaesth 15:61–66, 1990
84. Walker JJ, Johnstone J, Lloyd J, et al: The transfer of ketorolac tromethamine from maternal to foetal blood. Eur J Clin Pharmacol 34:509–511, 1988

85. Wall PD, Fitzgerald M: Effects of capsaicin applied locally to adult peripheral nerve: I. Physiology of peripheral nerve and spinal cord. Pain 11:363–377, 1981
86. Watson CPN, Evans RJ, Watt VR: Post-herpetic neuralgia and topical capsaicin. Pain 33:333–340, 1988
87. WHO Technical Report Series 775, Geneva, 1989
88. Wing LMH, Reid JL, Davies DS, et al: Pharmacokinetic and concentration effect relationships of clonidine in essential hypertension. Eur J Clin Pharmacol 12:463–469, 1977
89. Wischnik A, Manth SM, Lloyd J, et al: The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. Eur J Clin Pharmacol 36:521–524, 1989
90. Yaksh TL, Farb DH, Leeman SE, et al: Intrathecal capsaicin depletes substance P in the rat spinal cord and produces prolonged thermal analgesia. Science 206:481–483, 1979
91. Yee J, Bradley R, Stanski D, et al: A comparison of analgesic efficacy of intramuscular ketorolac tromethamine and meperidine in post-operative pain [abstract]. Clin Pharmacol Ther 39:237, 1986
92. Yee JP, Koshiver JE, Allbon C, et al: Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Pharmacotherapy 6:253–261, 1986
93. Yee JP, Waterbury LD: Ketorolac tromethamine is a new analgesic with efficacy comparable to morphine that does not bind to opioid receptors and has low addictive potential [abstract]. Clin Res 35:163A, 1987

Address reprint requests to

Mark S. Shulman, MD
Department of Anesthesiology
St. Elizabeth's Hospital of Boston
736 Cambridge Street
Boston, MA 02135

CURRENT CONCEPTS IN ACUTE PAIN CONTROL 0889-8537/92 $0.00 + .20

EPIDURAL AGENTS FOR POSTOPERATIVE ANALGESIA

Neal H. Badner, MD, FRCPC(C)

The application of intrathecal (spinal) or epidural medication to achieve postoperative analagesia was first reported in 1949 using local anesthestics.[56] However, it was the discovery of spinal opiate receptors in the late 1970s[135] that led to the popularity of the technique, as epidural morphine produced equal analgesia to that of local anesthetics, yet with fewer side effects.[22] The use of epidural morphine did lead to the occurrence of late respiratory depression, a serious though rare complication.[60] This has led investigators to use lipid-soluble narcotics, partial agonist-antagonist narcotics, narcotic and local anesthetic combinations, and most recently α_2-agonists such as clonidine, all in attempts to decrease the incidence of this side effect. This article summarizes the advantages and disadvantages of the spinal and epidural use of these agents in present clinical settings.

LOCAL ANESTHETICS

Local anesthetics have been injected into both the intrathecal and epidural spaces for surgical anesthesia since the early 1900s.[92] However, the duration of anesthesia even with the longer-acting agents, tetracaine intrathecally or bupivacaine epidurally, is no more than 3 to 4 hours. This is clearly insufficient for postoperative analgesia. The introduction of indwelling catheters into the epidural space allowed repeat dosing and hence postoperative use. The use of epidural local anesthesia for postoperative pain management has been reported following upper

---

From the Department of Anesthesiology, University of Western Ontario; and Acute Pain Service, University Hospital, London, Ontario, Canada

abdominal,[58, 123] lower abdominal,[39] thoracic,[31, 57] and orthopedic surgery.[111] Until recently catheters have not been used in the subarachnoid space for fear of postdural puncture headache or infection. With the introduction of 26- to 32-gauge catheters, and the subsequent low incidence of headache, continuous spinal anesthesia has been used for long operative procedures and recently for postoperative anlagesia following vascular procedures.[17]

In the previously quoted epidural studies the local anesthetics used were either lidocaine or, more commonly, bupivacaine. Like all local anesthestics, they are highly lipid-soluble agents with a negative log of dissociation constants of 8.1 for bupivacaine and 7.7 for lidocaine.[33] When deposited into the epidural space they rapidly diffuse through the dura and cerebrospinal fluid (CSF) to the spinal cord where blockade of neuronal transmission is the presumed site of action (Fig. 1). In increasing order of blockade, the small postganglionic sympathetic fibers are blocked most readily, followed by sensory, and lastly motor fibers. The degree of blockade depends on the concentration and volume of local anesthetic used. Clinically, intermittent doses of 5 to 10 mL of 0.5% bupivacaine have provided good analgesia, following either thoracotomies[56] or gastric surgery,[24, 123] and have decreased the use of mechanical ventilation following multiple rib fractures[36] when given through thoracic-level epidural catheters. The use of 8 to 12 mL through lumbar epidural catheters following gynecologic surgery also has been effective.[39, 113] Similarily, 1.5% lidocaine given through a thoracic epidural catheter provided good analgesia following abdominal surgery.[22] The duration of analgesia in these studies was, however, only 3 to 4 hours. To overcome this short duration of action one can use continuous infusions of local anesthetic, e.g., 3 to 10 mL/h of 0.25% or 5 to 15 mL/h of 0.125% bupivacaine. This has resulted in good analgesia following thoracotomies,[31] gastric bypass procedures,[24] cholecystectomies,[58] and knee joint replacements.[111] However, only the study by Raj et al[111] used an objective visual analogue scale to measure pain.

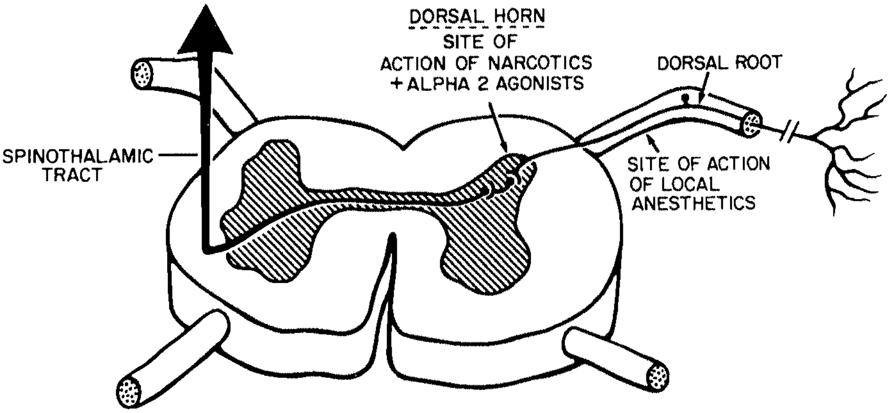


Figure 1. Cross-section of spinal cord showing the site of action of local anesthetics, narcotics, and alpha-2 agonists.

Possible beneficial effects on pulmonary and endocrine function have not been consistently demonstrated. Following upper abdominal surgery a single bolus of 1.5% lidocaine improved postoperative forced expiratory volume in 1 second,[22] yet repetitive boluses of 0.5% bupivacaine did not change physiologic dead space in percent of tidal volume, forced expiratory volume in 1 second, or forced vital capacity,[123] nor did an infusion of 0.25% bupivacaine improve ventilatory capacity or peak expiratory flow rate when compared with systemic morphine.[108] Though 1.5% lidocaine given through a lumbar catheter to upper abdominal surgery patients improved functional residual capacity from 78% of the preoperative value when in pain to 84% after injection and pain free,[130] 0.5% bupivacaine given to postoperative gastric bypass patients did not improve PaO_2 or the incidence of pulmonary complications[49] and did not change functional residual capacity and PaO_2 in postoperative lower abdominal surgery patients when compared with systemic narcotics.[39] Similarily, a continuous infusion of 0.25% bupivacaine did not improve PaO_2 or $AaDO_2$ following upper abdominal surgery when compared with systemic narcotics.[109] Conversely, Pflug et al[109] did show a decreased "convalescent time" in their epidural group of patients following upper abdominal surgery, and Buckley et al[24] showed a decreased incidence of pulmonary complications in morbidly obese patients undergoing abdominal surgery, who had received epidural local anesthesia postoperatively. Effects on the metabolic stress response to surgery, i.e., the ability to block the increase in cortisol, insulin, and glucagon, seems to depend on the location of surgery.[67] Patients undergoing lower abdominal surgery with epidural local anesthesia postoperatively did not have this hormonal increase,[113] whereas those undergoing upper abdominal surgery had elevated levels of cortisol, glucagon, and insulin in spite of T4 level of anesthesia from a postoperative epidural infusion of 0.5% bupivacaine.[69]

The major problem with postoperative analgesia from the epidural use of local anesthetics is the side effects that occur. These side effects relate to the mechanism of action, namely blocking sympathetic fibers causing hypotension, or motor fibers causing muscle weakness. When used following thoracotomies or upper abdominal surgery, all of the patients receiving intermittent boluses of 0.5% bupivacaine,[57] and over half of those receiving a continuous infusion of 0.25% bupivacaine[31, 109] developed hypotension requiring treatment. Of the patients who had undergone knee joint replacement and received 0.25% bupivacaine as a continuous epidural infusion,[111] over half had some motor block for the first 48 hours. As well as being troublesome on their own, both of these side effects limit the ablility to ambulate, which is usually one of the goals of good postoperative analgesia. For these reasons, though effective, the use of epidural local anesthesia has not become popular for postoperative analgesia. Recently, lower concentrations of bupivacaine (0.1%) are being combined with epidural opioids for use postoperatively.[77-80] This technique is discussed in the section entitled opioid-local anesthetic combinations.

As noted previously, postoperative continuous spinal anesthesia only recently has been reported in vascular patients.[17] Lidocaine, in concentrations of 0.5% to 2.0%, infused at 2 to 10 mL/h, provided excellent analgesia for all 10 patients, with only two requiring supplemental morphine. There was no evidence of hemodynamic instability or motor block; however, two of five patients in whom a 28-gauge catheter was used experienced pump occlusion difficulty. Further studies are obviously necessary to determine not only the optimal concentrations and infusion rates, but also the long-term safety of this technique.

OPIOIDS

Morphine

Morphine is the prototypical narcotic agonist. Its use in the epidural space was reported in 1979,[12] following the discovery of opioid receptors in the dorsal horn of the spinal cord.[135] Though initially debated, the site of action is thought to be due to activation of these receptors at the spinal level (Fig. 1).[32] Studies in orthopedic,[112] abdominal,[119] and thoracic surgery,[74] and cesarean section patients[62] have shown that epidural morphine produces better and longer lasting analgesia than smaller doses of intramuscular, intravenous, or patient-controlled analgesia (PCA) morphine. More importantly, epidural morphine leads to an improvement in forced expiratory volume in 1 second and forced vital capacity following upper abdominal[22] or thoracic surgery,[120] and a decrease in the incidence of myocardial ischemia and ectopy.[11] However, its use is unable to blunt the endocrine stress response to surgery.[61] When compared with local anesthetics, epidural morphine produces postoperative analgesia equal to that of epidural bupivacaine without causing hypotension or sensory and motor changes.[119, 127]

Unlike the other narcotics described in the following sections, it is relatively lipid insoluble, with an octanol/water coefficient of 1.42. This explains its slow penetration through the dura from the epidural space,[121] and hence its slow onset of 45 to 60 minutes.[22, 126] The corollary is that it is also slowly removed, leading to a long duration of action of 8 to 24 hours.[22, 51, 126] Dosages for upper abdominal surgery and thoracotomy patients are 5 to 10 mg,[22, 120, 125, 126] regardless of whether the catheter is inserted at a lumbar or thoracic level.[50] This is advantageous as thoracic epidural catheter insertion is technically more difficult and carries a risk of cord injury. Lower abdominal surgery, cesarean section, and orthopedic patients need doses of only 2 to 5 mg.[51, 62, 117, 125] To avoid repeat bolusing, a continuous infusion of a 0.1 mg/mL solution can be used at a rate of 4 to 6 mL/h. This has been done for thoracotomy and abdominal aneurysm patients with good results.[34, 74] However, using epidural infusions of shorter-acting agents allows quicker reversal on discontinuation and is therefore recommended.

Complications with this technique include nausea, vomiting, pruritis, urinary obstruction, and respiratory depression. Though serious, respiratory depression is rare. Three large studies reviewing roughly 15,000 patients found an incidence of less than 1%.[51, 60, 125] These studies found that when respiratory depression does occur, it usually involves elderly patients or the use of supplemental systemic narcotics. It appears to be centrally mediated as studies have shown epidural morphine to depress the ventilatory response to CO_2[68] and to increase the number of episodes of apnea.[118] The mechanism appears to result from the cephalad migration of morphine in CSF.[32] Because of epidural morphine's long duration of action, this can occur up to 24 hours after the last dose. Nausea and vomiting occur in 30% to 40% of patients and are also believed to be centrally mediated.[32] Urinary obstruction, with a 5% to 40% incidence, is due to bladder detrusor muscle dysfunction.[56] Pruritus, which is not due to histamine release, but possibly due to sensory input alteration in the dorsal horn, occurs 10% to 50% of the time and can be reversed with small doses of intravenous naloxone without inhibiting the analgesic effect.[90]

The long duration of action of morphine also applies to spinal use, meaning that a single intrathecal dose can provide postoperative analgesia for 24 hours or longer. As postoperative use of spinal catheters is only a recent phenomenon (see previous discussion), single-shot spinal application was the only technique, making spinal morphine an effective option. Spinal morphine has provided effective analgesia following thoracotomy,[99] abdominal aneurysmectomy,[35] herniorrhaphy,[66] cesarean section,[1] and major orthopedic surgery.[65] Because the morphine does not have to cross the dura, the dose is much lower. In the previous studies 0.5 to 1.0 mg was sufficient for upper abdominal and thoracic surgery and 0.25 to 0.5 mg for lower abdominal surgery. The major problem with this practice is that the side effects, though similar in nature to those for epidural use, occur much more frequently[60, 65] and outweigh the benefits.

Meperidine

Epidural use of meperidine was reported shortly after morphine.[52, 117] Though effective, its use has not become popular in North America, likely due to its similarity to the other lipid-soluble narcotics. Its octanol/water partition coefficient is roughly 40 times that of morphine, and therefore when given epidurally penetrates the dura quickly,[121] leading to an onset of analgesia in 15 to 30 minutes, but with a relatively short duration of action of 4 to 6 hours.[23, 52, 100, 117] This is a faster onset and shorter duration of action than morphine (see previous discussion), while, on the other hand, a little slower and longer than that for fentanyl and sufentanil (see following discussion). Dosing of 30 to 50 mg following cesarean section or lower abdominal surgery[23, 100, 121] and 50 to 100 mg after thoracic or upper abdominal surgery[51, 117, 126] produces analgesia equal to that of epidural morphine or fentanyl.[100, 117, 126]

Meperidine has the advantage of having local anesthetic properties and has been used as the sole anesthetic when given spinally.[104] The duration of spinal anesthesia is limited to 2 hours, thus postoperative use would necessitate a continuous infusion. This has not been reported at present. This local anesthetic effect does not appear to be present when used epidurally because Glynn et al[52] could not even detect sympathetic changes in the feet after 100 mg. Whether there is a synergistic effect when used epidurally in combination with local anesthetics has not been pursued as it has been with other epidural narcotics (see following). The use of both continuous spinal and epidural meperidine and local anesthetic combinations will likely be further explored in the future.

Fentanyl

Though epidural morphine provides good-to-excellent postoperative analgesia, the side effects, as noted previously, have led to the use of lipid-soluble narcotics. Theoretically, these agents are rapidly absorbed from the epidural space, thereby avoiding cephalad circulation and hence late respiratory depression. Fentanyl, which is 800 times more lipid soluble than morphine, is probably the most popular lipid-soluble narcotic in North America, and therefore has been investigated the most. For lower abdominal procedures doses of 50 to 100 μg are very effective when using a lumbar epidural catheter.[3, 30, 82, 94, 136] Following upper abdominal or thoracic surgery larger doses of 100 to 200 μg are required.[5, 75, 84] For these more major procedures the location of the epidural catheter, in the thoracic or lumbar spine, does not seem to matter if the optimal concentration of 10 μg/mL is used.[18] If a more concentrated solution is used as is necessary in epidural PCA, the epidural catheter should be placed adjacent to the necessary dermatomes.[19] Independent of these factors is the fact that epidural fentanyl has a rapid onset of analgesia of 15 to 30 minutes, but a short duration of only 2 to 5 hours.[3, 30, 82, 84, 94] Whether epidural fentanyl causes respiratory depression depends on the definition and measurement technique. If CO_2 response testing is employed, a dose of 200 μg given to preoperative patients will depress the slope of the CO_2 response curve,[98] whereas 100 μg in volunteers does not.[70] Clinically, postoperative patients monitored by arterial blood gas sampling[75, 84] or continuous end-tidal CO_2 analysis[81] have shown no incidences of respiratory depression. The few case reports that have documented respiratory depression from epidural fentanyl have been early in onset and almost always in conjunction with the use of systemic sedatives, there being no evidence of late-onset respiratory depression.[47] Of the minor side effects, pruritis is the most common, occurring in 30% to 50% of patients, with nausea and vomiting occurring much less frequently.[3, 82, 94]

Epidural fentanyl's short duration of action has led to the use of continuous epidural infusions. If the epidural catheter is placed adjacent to the appropriate dermatomes, good analgesia can be provided to postoperative thoracic, upper abdominal, or orthopedic surgical patients with 0.5 to 1.0 μg/kg/h, using a solution whose concentration is 10 μg/mL.[5, 9, 54, 132] With this technique patients do not develop significant systemic fentanyl levels[5] and have a similar incidence of side effects as do bolus epidural fentanyl patients.[54] However, this requires inserting catheters in the thoracic epidural space for thoracotomy or upper abdominal surgery patients. Lumbar epidural catheters can be used for thoracotomy or upper abdominal surgery patients; however, this requires the use of 1.0 to 1.5 μg/kg/h of fentanyl.[8, 13, 14] This in turn leads to systemic fentanyl concentrations of 1.0 to 2.0 ng/mL,[8] levels necessary for systemically administered fentanyl analgesia,[55] suggesting that this technique may be nothing more than a modified form of intravenous therapy. Three recent double-blind studies comparing infusions of fentanyl given either intravenously or epidurally to patients who required dosages of 1.5 μg/kg/h following either cesarean section,[45] orthopedic,[76] or thoracic surgery[102] found no difference in fentanyl requirements. This suggests that use of an epidural infusion of fentanyl requires insertion of the catheter adjacent to the necessary dermatomes.

Sufentanil

Sufentanil, the next-generation synthetic, phenylpiperidine opioid, has a lipid solubility roughly twice that of fentanyl. Its increased systemic potency and mu-receptor binding[73] led to hopes that it would provide analgesia similar to epidural fentanyl, but with a longer duration of action and fewer side effects. However, it has only fulfilled some of these expectations. Good analgesia, with an onset of 15 minutes or less and a duration slightly longer than fentanyl of 4 to 6 hours, has been obtained following cesarean section,[29, 82, 115] and orthopedic,[37] thoracic,[133] and abdominal surgery.[128] Initially, dosages of 50 to 75 μg were used, which led to significant early onset respiratory depression[124, 128, 133] as well as increased incidences of the minor side effects[82] or sedation,[29, 37] without increasing analgesia. This has led to the use of 30 to 50 μg following thoracic or upper abdominal surgery,[128, 133] through either lumbar or thoracic catheters, and 15 to 30 μg following cesarean section or orthopedic surgery.[29, 37, 82, 115] This leads to the observation that though systemic sufentanil is five to seven times as potent as fentanyl, when given epidurally, it is only twice as potent.[29] This may be due to increased nonspecific, nonreceptor uptake of sufentanil by other lipophilic neuronal tissues.[83]

As with fentanyl, the short duration of analgesia from epidural sufentanil has led to the use of continuous infusions. Dosing for thoracotomy or upper abdominal surgery patients is 0.15 to 0.30 μg/kg/h when using a 1.0 μg/mL solution.[15, 27, 40] It appears that catheter placement does not affect the dose if the dilute 1.0 μg/mL concentration is used.[40] The only study looking at systemic absorption from a continuous lumbar epidural infusion suggests that this is, however, important, because significant plasma concentrations were reported.[27]

Recently, Naulty et al[96] have reported that the addition of small doses (10–20 μg) of sufentanil to epidural morphine improved the onset time without increasing the side effects or decreasing the duration of action when given after cesarean section. Larger studies involving different patients are required to further assess this practice.

Alfentanil

This is the newest of the synthetic, phenylpiperidine mu-agonist narcotics. It is less lipid soluble than fentanyl but more so than morphine, yet also has a lower negative log of dissociation constant, giving it a rapid onset and short duration of analgesia when given systemically. There has been relatively little use of this agent epidurally; however, in the few studies to date it has been shown to have similar properties to epidural fentanyl, except for a shorter duration of action. A dose of 15 μg/kg produces equal analgesia to fentanyl in postoperative orthopedic or abdominal surgery patients, with an onset of 15 minutes or less and a duration of 60 to 90 minutes.[26, 28, 106] There was no change in respiratory rate or $Paco_2$ in postoperative patients,[26] however, the slope of the CO_2 reponse curve was depressed in volunteers.[106] The incidence of nausea, vomiting, and pruritus was no different than that of epidural fentanyl.[26] This agent also seems to require use as an epidural infusion,[28] yet offers no advantages over fentanyl, and at this time is therefore not widely used.

NARCOTIC AGONIST-ANTAGONISTS

There are several types of opioid receptors found in the brain and spinal cord, namely mu-, kappa-, and sigma-receptors. It is through activation of mu-receptors that epidural morphine and the other narcotics produce their effects: analgesia, pruritus, and urinary retention in the spinal cord level or nausea, vomiting, and respiratory depression in the brain stem. The κ opiate receptors are also associated with analgesia. The epidural use of combined κ-agonist, μ-antagonists, such as butorphanol and nalbuphine, therefore, should provide analgesia without the μ-receptor–mediated side effects. These agents have been used for postoperative analgesia following cesarean section, thoracotomies, and upper abdominal surgery.

They are both lipid-soluble agents, with an onset of action of 30 minutes for 1 to 4 mg of butorphanol,[2] and 15 minutes for 10 mg of nalbuphine.[86, 87] The duration of action is 2 to 4 hours for butorphanol,[2–4] and 4 to 8 hours for nalbuphine.[86, 87] The major advantage with these agents is that the incidence of the minor side effects of nausea, vomiting, and pruritis is almost zero.[2–4, 86–89, 97] Specifically for butorphanol, pruritis is significantly less than epidural morphine[2, 88, 101] and fentanyl.[3] The disadvantage is that the analgesia from their epidural use, though effective following cesarean section or upper abdominal surgery with butorphanol,[2–4, 88, 97, 101] or following upper abdominal surgery and thoracotomies with nalbuphine,[10, 46, 86, 87, 89] is clearly inferior to epidural morphine when compared in a random, double-blind fashion.[2, 10, 46] Also, both drugs when given epidurally produce marked sedation. This occurs in 50% to 90% of patients,[2, 86–89, 97] presumably due to simultaneous sigma opiate receptor stimulation. More important is the fact that epidural butorphanol has been shown to depress the CO_2 response curve when given to postcesarean section patients,[2] and epidurally nalbuphine has led to PaCO_2 greater than 50 in post-thoracotomy patients,[10] indicating that they also cause respiratory depression.

Attempts to use the κ-agonists together with other narcotics epidurally have not met with a large deal of success either. Butorphanol when combined with fentanyl either as a bolus following cesarean section[95] or as an infusion in a mixed group of patients[77] did not augment analgesia and markedly increased sedation. Similarily, nalbuphine when combined with epidural morphine, though increasing onset time, did not improve analgesia or the incidence of side effects.[131] However, a recent study did find that 3 mg of butorphanol combined with 4 mg of epidural morphine given to cesarean section patients significantly decreased the incidence of pruritus, nausea, and oxygen desaturation, while maintaining similar analgesia without causing sedation.[71]

In spite of the low incidence of minor side effects, which can be annoying to patients, the high incidence of sedation coupled with the ability to cause respiratory depression, and the inferior analgesia that they produce, has prevented the κ-agonists from becoming popular for postoperative epidural use. If butorphanol combined with epidural morphine consistently produces results as noted previously,[71] it would constitute a significant improvement in epidural analgesia and would warrant recommendation for general use.

OPIOID-LOCAL ANESTHETIC COMBINATIONS

Efforts to decrease the dosage and therefore limit the systemic absorption of epidural narcotics has led to the use of epidural infusions of a mixture of narcotic and low-dose local anesthetic, usually bupivacaine. Theoretically, as the two drugs act by different mechanisms their effects should be synergistic. Therefore, this should allow decreased amounts of each drug and thereby minimize the incidence of side effects, which have been described previously. This has been tried with morphine using 0.1 mg/mL combined with 0.1% bupivacaine. Though effective, the combination was in fact no better than the same infusion of epidural morphine alone in terms of analgesia, total narcotic requirements, nausea, or pruritus following either thoracotomy[74] or upper abdominal surgery.[34] Similarily, 0.125% bupivacaine did not improve postoperative analgesia from 3 or 5 mg of epidural morphine when given to cesarean section patients.[38] Subsequently, epidural infusions of fentanyl (10 μg/mL) or sufentanil (1 μg/mL) and identical low-dose (0.1%) bupivacaine have been shown to be effective for postoperative pain management following various surgical procedures.[48, 59, 78–80] However, none of these studies have been double blind or randomized. Several such recently completed studies, using the same fentanyl-bupivacaine concentrations, found no synergism in either knee joint replacement or abdominal surgery patients.[6, 7, 16] In an analogous study, epidural infusions of hydromorphone and 0.08% bupivacaine were found to be no more beneficial than hydromorphone alone for postcesarean section pain.[44]

The use of 0.1% bupivacaine may simply be insufficient to offer an advantage to the postoperative patient population. This is different than findings in obstetric patients in which several narcotics including fentanyl,[44, 122, 134] sufentanil,[110, 134] alfentanil,[134] and even butorphanol[64] when mixed with bupivacaine, either 0.125% or 0.25%, supplied superior analgesia to laboring women. The proviso is that labor pain is different from postoperative pain because it is not relieved by epidural narcotics alone,[25] and comparisons were made with plain bupivacaine and not plain fentanyl. The only double-blind study claiming beneficial effects of low-dose (0.125%) bupivacaine added to an epidural narcotic infusion, in this case to diamorphine following hysterectomy, used such high infusion rates that all patients developed a T6–T8 sensory level, and 70% of them developed urinary retention.[72] Morphine combined with a much higher concentration of 0.5% bupivacaine given as an infusion resulted in impressive mean pain scores of 0 for a 16-hour study period.[63] The patients in this study did however all have a high thoracic sensory block, which as noted earlier is not ideal. Further studies using narcotic and local anesthetic combinations, with concentrations of bupivacaine between 0.1% and 0.5%, are therefore obviously needed to determine the optimal concentrations to achieve the desired improved analgesia and decreased side effects.

α_2-AGONISTS

The newest means of providing postoperative analgesia is through the use of spinal/epidural α_2-agonists, namely clonidine. Clonidine activates postjunctional α_2-adrenoceptors in the dorsal horn, thereby inhibiting the firing of nociceptive neurons (Fig. 1).[41] Most studies using spinal/epidural clonidine have involved animals; however, because it is now available in aqueous form in Europe and is soon to be released in North America for investigational purposes, further human studies will be forthcoming.

Clonidine is a lipid-soluble drug with an octanol/water partition coefficient approximately equal to that for meperidine.[21] It has a rapid onset of action within 15 to 30 minutes[21, 53] and a short duration of action of 3 to 4 hours,[21] making it similar to the lipid-soluble narcotics. For this reason most studies involve the use of catheters placed in dermatomes adjacent to those of the surgical wound and incorporate continuous infusions. The majority of studies at present have involved epidural use.

Conflicting results on the analgesic efficacy of epidural clonidine have occurred, possibly relating to the lack of full-dose response information. Gordh,[53] using a dose of 3 μg/kg through a thoracic epidural catheter, found no difference in immediate postoperative meperidine use administered by PCA in postthoracotomy patients when compared with saline placebo, and 75 μg was insufficient for upper abdominal surgery.[89] Yet Petit et al,[108] in an oddly timed study, using a lumbar epidural catheter, gave 2 μg/kg as the sole analgesic to total esophagectomy patients from the 18th to 42nd postoperative hours with good results. Bonnet et al,[21] using a dose of 2 μg/kg through a lumbar epidural catheter to post–knee joint replacement patients, markedly improved visual analogue scale scores for 3 to 4 hours in comparison with saline, and, in the only double-blind comparison with epidural morphine, 150 μg of epidural clonidine produced equal analgesia and pulmonary function (forced expiratory volume in 1 second) as did 4 mg of epidural morphine given to hysterectomy patients.[81] These doses are much lower than the 700 to 900 μg (approximately 10–15 μg/kg) used in a recently completed open-labeled study involving postoperative abdominal and knee replacement patients.[42] These larger doses provided better and longer analgesia, decreased morphine usage, and decreased side effects when compared with 100 to 300 μg and 400 to 600 μg dosages. Similarily an 800-μg bolus followed by a 20 μg/h infusion led to decreased morphine use over 24 hours when compared with saline.[85] However, these dosages led to systemic clonidine levels in the 2 to 3 ng/mL range, which are double the amount that others have reported,[20, 53, 108] suggesting a systemic effect. Supporting this is the recent finding that 2 μg/kg of clonidine given either epidurally or intramuscularily produced equal analgesia, with serum levels of roughly 1 ng/mL.[20] Obviously, further studies will have to be performed to determine the optimal dosages.

As with both local anesthetics and narcotics there are side effects that may limit clinical use. Sedation, described almost always as drowsiness, has occurred in most patients[20, 21, 42] and is thought to be secondary to brain stem α_2 action.[21] Hypotension, due to the inhibition of spinal sympathetic outflow,[43] has occurred in all the patients in all the studies, varying from 20% to 30%,[20, 21, 42, 53, 85, 105, 108] though only those receiving 400 to 600 μg in the open-labeled study required treatment. Heart rate is also decreased in almost all patients,[20, 21, 42, 81, 85, 108] though none have required treatment. Respiratory effects may be similar to epidural opioids as the 3 μg/kg dose and the open-labeled doses up to 900 μg did not change pH, or PaCO_2,[42, 53] yet 300 μg depressed the slope of the CO_2 response curve,[105] implying depression of respiratory control.

In light of these side effects when used alone, epidural clonidine may ultimately be used in combination with a narcotic. Recent studies using epidural clonidine combined with fentanyl,[116] sufentanil,[129] and morphine[91, 107] have shown improved analgesia and decreased supplemental narcotic usage, though this was not true for nalbuphine.[89] However, blood pressure and heart rate still decreased significantly in the combination groups when compared with the groups receiving epidural narcotic alone. These side effects may be eliminated with different dosing combinations, and further clinical studies are necessary. Also, current laboratory research involves α_2-receptor subtypes, α_{2A} and α_{2B}, which may differentiate analgesia and side effects, as well as the development of a lipid-insoluble α_2-agonist.[41]

SUMMARY

This article has discussed the current use of intrathecal and epidural agents for the relief of postoperative pain. Local anesthetics, though effective, produce excessive side effects. Narcotics, namely morphine, are widely used, and occasionally produce respiratory depression. Lipid-soluble narcotics may reduce the incidence of this complication, while the partial agonist-antagonists do not produce effective analgesia. Combinations of these drugs with local anesthetics may produce the best results, though the optimal concentrations and dosages have not been determined. The most recently tried agent, clonidine, an α_2-agonist, also is effective, though the proper dosing regimen has not been determined, and sedation remains a problem.

References

1. Abboud TK, Dror A, Mosaad P, et al: Mini-dose intrathecal morphine for the relief of post-cesarean section pain. Anesth Analg 67:137, 1988
2. Abboud TK, Moore M, Zhu J, et al: Epidural butorphanol or morphine for the relief of post-cesarean section pain: Ventilatory responses to carbon dioxide. Anesth Analg 66:887, 1987
3. Ackerman WE, Juneja MM, Colclough GW: A comparison of epidural fentanyl, buprenorphine and butorphanol for the management of post cesarean section pain. Anesthesiology 39:A401, 1988
4. Ackerman WE, Juneja MM, Kaczorowski DM, et al: A comparison of the incidence of pruritus following epidural opioid administration in the parturient. Can J Anaesth 36:388, 1989
5. Ahuja BR, Strunin L: Respiratory effects of epidural fentanyl. Anaesthesia 40:949, 1985
6. Badner NH, Komar WE, Rajasingham M, et al: 0.1% bupivacaine does not improve postoperative epidural fentanyl analgesia following abdominal or thoracic surgery. Can J Anaesth 38 (suppl):A117, 1991
7. Badner NH, Reimer EJ, Komar WE, et al: Low dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. Anesth Analg 72:337, 1991
8. Badner NH, Sandler AN, Koren G, et al: Lumbar epidural fentanyl infusions for

post-thoracotomy patients: Analgesic, respiratory, and pharmacokinetic effects. J Cardiothoracic Anesth 4:543, 1990

9. Bailey PW, Smith BE: Continuous epidural infusion of fentanyl for postoperative analgesia. Anaesthesia 35:1002, 1980
10. Baxter AD, Laganiere S, Samson B, et al: A dose-response study of nalbuphine for post-thoracotomy epidural analgesia. Can J Anaesth 38:125, 1991
11. Beattie WS, Buckley DN, Forrest JB: Reduction of significant cardiac morbidity by epidural morphine in non-cardiac surgery. Anesthesiology 73:A71, 1990
12. Behar M, Magora F, Olshwang D, et al: Epidural morphine in treatment of pain. Lancet 1:527, 1979
13. Bell SD, Berman R, Ensalada L: The use of continuous lumbar epidural fentanyl for post-operative pain relief in thoracotomies. Can J Anaesth 35:S112, 1988
14. Bell SD, Levette A, Larijani GE: The use of continuous lumbar epidural fentanyl for post operative pain relief in abdominal aortic aneurysms. Anesthesiology 67:A234, 1987
15. Bell SD: The use of continuous lumbar epidural sufentanil for postoperative pain relief in thoracotomies. Reg Anesth 14:2S:33, 1989
16. Berde CB, Sethna NF, Yemen TA, et al: Continuous epidural bupivacaine fentanyl infusions in children following ureteral reimplantation. Anesthesiology 73:A1128, 1990
17. Bevacqua Bk, Slucky AV, Adusumilli SB: Post-operative analgesia with continuous intrathecal lidocaine infusion. Anesthesiology 73:A833, 1990
18. Birnbach DJ, Johnson MD, Arcario T, et al: Effect of diluent volume on analgesia produced by epidural fentanyl. Anesth Analg 68:808, 1989
19. Bodily MN, Chamberlain DP, Ramsey, et al: Lumbar versus thoracic epidural catheter for post-thoracotomy analgesia. Anesthesiology 71:A1146, 1989
20. Bonnet F, Boico O, Rostaing S, et al: Clonidine induced analgesia in postoperative patients: Epidural versus intramsucular administration. Anesthesiology 72:423, 1990
21. Bonnet F, Boico O, Rostaing S, et al: Postoperative analgesia with extradural clonidine. Br J Anaesth 63:465, 1989
22. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. Anesth Analg 59:473, 1980
23. Brownridge P, Frewin DB: A comparative study of techniques of postoperative analgesia following caesarean section and lower abdominal surgery. Anaesth Intens Care 13:123, 1985
24. Buckley FP, Robinson NB, Simonowitz DA, et al: Anaesthesia in the morbidly obese. Anaesthesia 38:840, 1983
25. Carrie IES, O'Sullivan GM, Leeglobin R: Epidural fentanyl in labour. Anesthesia 36:965, 1981
26. Chauvin M, Salbaing J, Perrin D, et al: Clinical assessment and plasma pharmacokinetics associated with intramuscular or extradural alfentanil. Br J Anaesth 57:886, 1985
27. Cheng EY, Koebert RF, Hopwood M, et al: Continuous epidural sufentanil for postoperative analgesia. Anesthesiology 67:A233, 1987
28. Chrubasik J, Wust H, Schulte-Monting J, et al: Relative analgesic potency of epidural fentanyl, alfentanil, and morphine in treatment of postoperative pain. Anesthesiology 68:929, 1988
29. Cohen SE, Tan S, White PF: Sufentanil analgesia following cesarean section: Epidural versus intravenous administration. Anesthesiology 68:129, 1988
30. Colburn N, Mandell G; Rudy T: Epidural fentanyl for post-vaginal delivery pain. Anesthesiology 73:A986, 1990
31. Conacher ID, Paes ML, Jacobson L, et al: Epidural analgesia following thoracic surgery. Anaesthesia 38:546, 1983
32. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. Anesthesiology 61:276, 1984
33. Covino BG: Basic and clinical pharmacology of local anesthetic drugs. *In* Miller RD (ed): Anesthesia, ed 2. New York, Churchill Livingstone, 1986, p 985
34. Cullen ML, Staren ED, El-Ganzouri A, et al: Continuous epidural infusion for analgesia after major abdominal operations: A randomized, prospective, double-blind study. Surgery 98:718, 1985

35. Davis I: Intrathecal morphine in aortic aneurysm surgery. Anaesthesia 42:491, 1987
36. Dittman M, Steenblock U, Kranzlin M, et al: Epidural analgesia or mechanical ventilation for multiple rib fractures. Intensive Care Med 8:89, 1982
37. Donadoni R, Rolly G, Noordum H, et al: Epidural sufentanil for postoperative pain relief. Anaesthesia 40:634, 1985
38. Douglas MJ, McMorland GH, Janzen JA: Influence of bupivacaine as an adjuvant to epidural morphine for analgesia after cesarean section. Anesth Analg 67:1138, 1988
39. Drummond GB, Littlewood DG: Respiratory effects of extradural analgesia after lower abdominal surgery. Br J Anaesth 49:999, 1977
40. Duckett JE, McDonell T, Zebrowski M, et al: Lumbar versus thoracic continuous epidural sufentanil for postoperative analgesia after upper abdominal surgery. Anesth Analg 66:S45, 1987
41. Eisenach J: Alpha-2 adrenergic agonists. 1990 ASA Refresher Course Lectures 126:1–4, 1990
42. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. Anesthesiology 71:640, 1989
43. Eisenach JC: Site of intrathecal clonidine induced hypotension. Anesthesiology 73:A754, 1990
44. Elliot RD: Continuous infusion epidural anaesthesia for obstetrics: Bupivacaine versus bupivacaine-fentanyl mixture. Can J Anaesth 38:303, 1991
45. Ellis DJ, Millar WL, Reisner LS: A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology 72:981, 1990
46. Etches RC, Sandler AN: Analgesic effects of epidural nalbuphine in post-thoracotomy patients. Can J Anaesth 36:S156, 1989
47. Etches RC, Sandler AN, Daley MD: Respiratory depression from spinal opioids. Can J Anaesth 36:165, 1989
48. Fisher R, Lubenow T, Licega A, et al: Comparison of continous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of post-operative pain. Anesth Analg 67:559, 1988
49. Fox GS, Whalley DG, Bevan DR: Anaesthesia for the morbidly obese. Br J Anaesth 53:811, 1981
50. Fromme LJ, Steidl LJ, Danielson DR: Comparison of lumbar and thoracic epidural morphine for relief of post-thoracotomy pain. Anesth Analg 64:454, 1985
51. Fuller JG, McMorland GH, Douglas MJ, et al: Epidural morphine for analgesia after caesarean section: A report of 4880 patients. Can J Anaesth 37:636, 1990
52. Glynn CJ, Mather LE, Cousins MJ, et al: Peridural meperidine in humans. Anesthesiology 55:520, 1981
53. Gordh T: Epidural clonidine for treatment of postoperative pain after thoracotomy. A double-blind placebo controlled study. Acta Anaesthesiol Scand 32:702, 1988
54. Gough JD, Williams AB, Vaughan RS, et al: The controp of post-thoracotomy pain. A comparative evaluation of thoracic epidural fentanyl infusions and cryo-analgesia. Anaesthesia 43:780, 1988
55. Gourlay GK, Kowalski SR, Plummer JL, et al: Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329, 1988
56. Gregg R: Spinal analgesia; management of postoperative pain. Anesthesiol Clin North Am 7:79, 1989
57. Griffiths DPG, Diamond AW, Cameron JD: Postoperative extradural analgesia following thoracic surgery: A feasibility study. Br J Anaesth 47:48, 1975
58. Griffiths DPG: Postoperative pain prevention by continuous epidural infusion. Anaesthesia 36:214, 1981
59. Guillen JC, Ragi J, Brugueralle B, et al: Continuous thoracic epidural analgesia for 5 days: Clinical and plasma evaluation. Anesthesiology 69:A404, 1988
60. Gustafsson LL, Schildt B, Jacobsen KJ: Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. Br J Anaesth 54:479, 1982
61. Hakanson E, Rutberg H, Jorfeldt L, et al: Effects of the extradural administration of morphine or bupivacaine, on the metabolic response to upper abdominal surgery. Br J Anaesth 57:394, 1985

62. Harrison DM, Sinatra R, Morgese L, et al: Epidural narcotic and patient-controlled analgesia for post-cesarean pain relief. Anesthesiology 68:454, 1988
63. Hjortso NC, Lund C, Mogenson T, et al: Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. Anesth Analg 65:1033, 1986
64. Hunt CO, Naulty JS, Malinow AM, et al: Epidural butorphanol—Bupivacaine for analgesia during labour and delivery. Anesth Analg 68:323, 1989
65. Jacobsen L, Chabal C: Intrathecal morphine: Efficacy, duration, optimal dose and side effects. Anesth Analg 67:S102, 1988
66. Katz J, Nelson W: Intrathecal morphine for postoperative pain relief. Reg Anesth 6:1, 1981
67. Kehlet H: Epidural analgesia and the endocrine-metabolic response to surgery. Acta Anaesthesiol Scand 28:125, 1984
68. Knill RL, Clement JL, Thompson WR: Epidural morphine causes delayed and prolonged ventilatory depression. Can Anaesth Soc J 28:537, 1981
69. Kossman B, Volk E, Spilkes ED, et al: Influence of thoracic epidural analgesia on glucose, cortisol, insulin and glucagon responses to surgery. Reg Anesth 7:107, 1982
70. Lam AM, Knill RL, Thompson WR, et al: Epidural fentanyl does not cause delayed respiratory depression. Can Anaesth Soc J 30:S78, 1983
71. Lawhorn CD, McNitt JD, Fibuch EE, et al: Epidural morphine with butorphanol for postoperative analgesia after cesarean delivery. Anesth Analg 72:53, 1991
72. Lee A, Simpson D, Whitfield A, et al: Postoperative analgesia by continuous extradural infusion of bupivicaine and diamorphine. Br J Anaesth 60:845, 1988
73. Leysen JE, Gommeran W, Niemegeers C: [^{3}H]-sufentanil a superior ligand for μ-opiate receptor binding properites and regional distribution in rat brain and spinal cord. Eur J Pharmacol 87:209, 1983
74. Logas WG, El-Baz N, El-Ganzouri A, et al: Continuous thoracic epidural analgesia for post-operaive pain relief following thoracotomy: A randomized prospective study. Anesthesiology 67:787, 1987
75. Lomessy A, Magnin C, Viale JP, et al: Clinical advantages of fentanyl given epidurally for postoperative analgesia. Anesthesiology 61:466, 1984
76. Loper KA, Ready LB, Downey M, et al: Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 70:72, 1990
77. Lubenow T, Durrani Z, Ivankovich A: Evaluation of continuous epidural fentanyl/butorphanol infusion for postoperative pain. Anesthesiology 73:A800, 1990
78. Lubenow TR, Fischer RL, Besser P, et al: Comparison of continuous epidural infusions of sufentanil-bupivicaine with morphine-bupivacaine. Anesthesiology 69:A397, 1988
79. Lubenow TR, Wong J, McCarthy RJ, et al: Prospective evaluation of continuous epidural narcotic-bupivicaine infusions in 1000 patients. Anesthesiology 69:A389, 1988
80. Lubenow TR, Wong J, McCarthy RJ, et al: Prospective evaluation of continuous epidural narcotic-bupivicaine infusions in 1500 postoperative patients. Reg Anesth 14:2S:32, 1989
81. Lund C, Qvitzau S, Greulich A, et al: Comparison of the effects of extradural clonidine with those of morphine on postoperative pain, stress responses, cardiopulmonary function and motor and sensory block. Br J Anaesth 63:516, 1989
82. Madej TH, Strunin L: Comparison of epidural fentanyl with sufentanil. Anaesthesia 42:1156, 1987
83. McQuay HJ, Sullivan AF, Smallman K, et al: Intrathecal opioids, potency and lipophilicity. Pain 36:111, 1989
84. Melendez JA, Cirella VN, Delphin ES: Lumbar epidural fentanyl analgesia after thoracic surgery. J Cardiothorac Anesth 3:150, 1989
85. Mendez RM, Eisenach JC, Kashtan K: Epidural clonidine analgesia following cesarean section. Anesthesiology 73:848, 1990
86. Mok MS, Lippman M, Wang JJ, et al: Efficacy of epidural nalbuphine in postoperative pain control. Anesthesiology 61:A187, 1984
87. Mok MS, Louie BW, Hwong BF, et al: Epidural nalbuphine for the relief of pain after thoracic surgery. Anesth Analg 64:S58, 1985

88. Mok MS, Tsai YJ, Ho WM, et al: Efficacy of epidural butorphanol compared to morphine for the relief of postoperative pain. Anesthesiology 65:A175, 1986
89. Mok MS, Wang JJ, Chan JH, et al: Analgesic effect of epidural clonidine and nalbuphine in combined use. Anesthesiology 69:A398, 1988
90. Morgan M: Therational use of intrathecal and extradural opioids. Br J Anaesth 63:165, 1989
91. Motsch J, Graber E, Ludwig K: Addition of clonidine enhances postoperative analgesia from epidural morphine: A double-blind study. Anesthesiology 73:1067, 1990
92. Murphy TM: Spinal, epidural and caudal anesthesia. *In* Miller RD (ed): Anesthesia, ed 2. New York, Churchill Livingstone, 1986, p 1061
93. Naulty JS, Barnes D, Becker R, et al: Continuous subarachnoid sufentanil for labour analgesia. Anesthesiology 73:A964, 1990
94. Naulty JS, Datta S, Ostheimer GW, et al: Epidural fentanyl for postcesarean delivery pain management. Anesthesiology 63:694, 1985
95. Naulty JS, Labove P, Datta S, et al: Epidural butorphanol/fentanyl for post cesarean delivery analgesia. Anesthesiology 67:A463, 1987
96. Naulty JS, Parmet J, Pate A, et al: Epidural sufentanil and morphine for post-cesarean delivery analgesia. Anesthesiology 73:A965, 1990
97. Naulty JS, Weintraub S, McMahon J, et al: Epidural butorphanol for post-cesarean delivery pain management. Anesthesiology 61:A415, 1984
98. Negre I, Guerneron JP, Ecoffey C, et al: Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. Anesth Analg 66:707, 1987
99. Nordberg G, Hedner T, Mellstrand T, et al: Pharmacokinetic aspects of intrathecal morphine analgesia. Anesthesiology 60:448, 1984
100. Paech MJ: Epidural pethidine or fentanyl during caesarean section: A double-blind comparison. Anaesth Intensive Care 17:157, 1989
101. Palacios QT, Jones MM, Hawkins JL, et al: Post caeserean section analgesia: A comparison of epidural butorphanol and morphine. Can J Anaesth 38:24, 1991
102. Panos L, Sandler AN, Stringer DG, et al: Epidural vs intravenous fentanyl infusions in postthoracotomy patients: Analgesic and pharmacokinetic effects. Anesthesiology 73:A831, 1990
103. Parker RK, Baron M, Helfer DC, et al: Use of epidural PCA for post-operative pain management: Effect of local anesthetic on the opiod requirement. Anesth Analg 70:S297, 1990
104. Patel D, Janardhan Y, Merai B, et al: Comparison of intrathecal meperidine and lidocaine in endoscopic urological procedures. Can J Anaesth 37:567, 1990
105. Penon C, Ecoffey C, Cohen SE: Ventilatory effects of epidural clonidine. Anesthesiology 71:A649, 1989
106. Penon C, Negre I, Ecoffey C, et al: Analgesia and ventilatory response to carbon dioxide after intramuscular and epidural alfentanil. Anesth Analg 67:313, 1988
107. Petit J, Oksenhendler G, Colas G, et al: Comparison of the effects of morphine, clonidine and a combination of morphine and clonidine administered epidurally for postoperative analgesia. Anesthesiology 71:A647, 1989
108. Petit J, Oksenhendler G, Colas G, et al: Pharmokinetics and effects of epidural clonidine in acute postoperative pain. Reg Anesth 14:2S:43, 1989
109. Pflug AE, Murphy TM, Butler SH, et al: The effects of postoperative peridual analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8, 1974
110. Phillips G: Continuous infusion epidural analgesia in labor: The effect of adding sufentanil to 0.125% bupivacaine. Anesth Analg 67:422, 1988
111. Raj PP, Knarr DC, Vigdorth E, et al: Comparison of continuous epidural infusion of a local anesthetic and administration of systemic narcotics in the management of pain after total knee replacement surgery. Anesth Analg 66:401, 1987
112. Reiz S, Ahlin J, Ahrenfeldt B, et al: Epidural morphine for postoperative pain relief. Acta Anaesth Scand 25:111, 1981
113. Rem J, Moller IW, Brandt MR, et al: Influence of epidural analgesia on postoperative changes in various serum enzyme patterns and serum bilirubin. Acta Anaesth Scand 25:142, 1981

114. Renaud B, Brichant JF, Clergue F, et al: Ventilatory effects of continuous epidural infusion of fentanyl. Anesth Analg 67:971, 1988
115. Rosen MA, Dailey PA, Hughes SC, et al: Epidural sufentanil for postoperative analgesia after cesarean section. Anesthesiology 69:448, 1988
116. Rostaing S, Bonnet F, Levron JC, et al: Effect of epidural clonidine on epidural fentanyl analgesia and pharmacokinetics in postoperative patients. Anesthesiology 73:A779, 1990
117. Rutter DV, Skewes DG, Morgan M: Extradural opioids for postoperative analgesia. Br J Anaesth 53:915, 1981
118. Sandler AN, Chovaz P, Whiting W: Respiratory depression following epidural morphine: A clinical study. Can Anaesth Soc J 33:542, 1986
119. Scheinin B, Asantila R, Orko R: The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. Acta Anaesth Scand 31:161, 1987
120. Shulman M, Sandler AN, Bradley JW, et al: Postthoracotomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 61:569, 1984
121. Sjostrom S, Hartvig P, Persson MP, et al: Pharmacokinetics of epidural morphine and meperidine in humans. Anesthesiology 67:877–888, 1987
122. Skerman JH, Thompson BA, Goldstein MT, et al: Combined continuous epidural fentanyl and bupivicaine in labour: A randomized study. Anesthesiology 63:A450, 1985
123. Spence AA, Smith G: Postoperative analgesia and lung function: A comparison of morphine with extradural block. Br J Anaesth 43:144, 1971
124. Stanton-Hicks MDA, Gielen M, Hasenbos M, et al: High thoracic epidural with sufentanil for post-thoracotomy pain. Reg Anesth 13:62, 1988
125. Stenseth R, Sellevold O, Breivik H: Epidural morphine for postoperative pain: Experience with 1085 patients. Acta Anaesthesiol Scand 29:148, 1985
126. Torda TA, Pybus DA: Comparison of four narcotic analgesics for extradural analgesia. Br J Anaesth 54:291, 1982
127. Torda TA, Pybus DA: Extradural administration of morphine and bupivacaine. Br J Anaesth 56:141, 1984
128. Van der Auwera D, Verborgh C, Camu F: Analgesic and cardiorespiratory effects of epidural sufentanil and morphine in humans. Anesth Analg 66:999, 1987
129. Vercauteren M, Meese G, Lauwers E, et al: Addition of clonidine potentiates postoperative analgesia of epidural sufentanil. Anesth Analg 70:S5, 1990
130. Wahba WM, Don HF, Craig DB: Post-operative epidural analgesia: Effects on lung volumes. Can Anaesth Soc J 22:519, 1975
131. Wang JJ, Mok MS, Lippman M: Analgesic effect of epidural morphine and nalbuphine in combined use. Anesthesiology 71:A703, 1989
132. Welchew EA, Thornton JA: Continuous thoracic epidural fentanyl. Anaesthesia 37:309, 1982
133. Whiting WC, Sandler AN, Lau LC, et al: Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. Anesthesiology 69:36, 1988
134. Wilhite AO, Blass NH: Comparison of analgesic efficacy of alfentanil, fentanyl, and sufentanil in continuous epidural infusions of 0.125% bupivacaine for labor and delivery. Anesthesiology 71:A902, 1989
135. Yaksh TL: Spinal opiate analgesia: Characteristics and principles of action. Pain 11:293, 1981
136. Yu PYH, Gambling DR, McMorland GH: A comparative study of patient controlled epidural fentanyl and single dose epidural morphine for post-caesarean section analgesia. Can J Anaesth 36:S55, 1989

Address reprint requests to

Neal H. Badner, MD
Director, Acute Pain Service
University Hospital
339 Windermere Road
London, Ontario
Canada N6A 5A5

0889-8537/92 $0.00 + .20

REGIONAL AND LOCAL BLOCK OF ACUTE PAIN

Larry Panos MD, FRCPC,
and Anthony L. Panos MD, MSc, FRCSC

Regional anesthetic techniques have gained widespread acceptance as an additional method for the management of acute pain. The aim of administering local anesthetic agents either via intermittent bolus or continuous infusion is to block sensory neural pathways. In many acutely painful conditions the majority of nociceptive stimuli arise peripherally and thus, regional anesthesia can often result in profound analgesia in these patients.

The use of regional anesthetic techniques for the management of postoperative pain has long been known and used by anesthesiologists to provide potentially intense, if somewhat brief, analgesia. Many practitioners frequently use some form of regional blockade to provide for a smooth emergence from general anesthesia for various surgical procedures. However, reviewing the literature there are few controlled trials (i.e., prospective, randomized, double-blind studies) of these techniques that could provide a rational basis for establishing the benefits of these blocks.

Several recent reviews of regional blockade of pain have concentrated largely on central neural axis blockade (epidural or intrathecal) or local anesthetic pharmacology[48, 85, 113] and regional techniques. In this article we review the use of local anesthetic blockade on peripheral nerves (major plexus, major and minor peripheral nerve blocks) in the management of acute pain. Central neuraxial blockade (epidural and intrathecal) is discussed in another article in this volume. Techniques of standard nerve blocks, their indications, and complications are well described elsewhere[17, 57] and are beyond the scope of this review.

From the Acute Pain Service, Department of Anaesthesia, Toronto General Division, The Toronto Hospital; and Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada

LOCAL ANESTHETIC WOUND INFILTRATION

The etiology of pain experienced in the postoperative period is not only due to the surgical wound, but is often multifactorial. Visceral pain, nasogastric tubes, coexisting painful pathology (e.g., bed sores), anxiety, and emotional components contribute to the total suffering experience. Nevertheless, wound infiltration with local anesthetic has been reported to significantly decrease postoperative pain and systemic analgesic requirements.[67, 102] Although initially reported over 40 years ago,[8] there has been a recent resurgence of interest in acute pain management using newer long-lasting local anesthetics for wound infiltration to control postoperative pain.

There are basically two approaches that have been tried. One is to simply infiltrate the wound directly at the time of surgical closure, and the other is to leave an indwelling catheter within one of the wound layers so that it can be used postoperatively for the intermittent, or continuous, infusion of anesthetic agents. The indwelling catheter should potentially offer a longer duration of analgesia.

Patel et al[69] instilled 50 mL of 0.25% bupivacaine in patients who had undergone upper abdominal incisions for cholecystectomy and found that, as well as decreasing the narcotic requirement, these patients also had improved pulmonary function. Patients who had received wound infiltration with bupivacaine had significantly higher values for arterial PO_2, forced vital capacity, and forced expiratory volume in 1 second. Upper abdominal surgery has long been known to result in altered respiratory mechanics and to be associated with a higher incidence of pulmonary complications postoperatively. Patel's group found 12 of 23 patients in the placebo group developed roentgenographic atalectasis as compared with only 3 of 17 patients who had recieved bupivacaine wound infiltration.

Improved analgesia plus decreased narcotic usage has been found in patients undergoing excisional breast biopsy[67] and cholecystectomy[59, 68, 102] with local anesthetic wound perfusion. Moss and his colleagues[59] found that, by combining immediate duodenal feeding via nasogastric tube and infiltrating peritoneum, fascia, subcutis, and skin with 40 to 50 mL of 0.5% bupivacaine in patients undergoing cholecystectomy, 93% of their patients could be discharged within 24 hours, and 81% did not require any narcotic.

As well as decreasing narcotic usage and pain scores, Partridge and Stabile[68] found that local anesthetic wound infiltration decreased postanesthetic care unit stay.

Many different dosing regimens have been recommended, but one reasonable schedule that we have found useful is listed in Table 1.[88]

In a randomized double-blind study, Tverskoy and colleagues[108] compared general anesthesia, spinal anesthesia, and general anesthesia combined with local wound infiltration in patients undergoing inguinal herniorrhaphy. As well as finding improved immediate postoperative analgesia in the wound infiltration group, these investigators found

Table 1. ONE COMMONLY USED DOSING SCHEDULE FOR LOCAL WOUND INFILTRATION WITH LOCAL ANESTHETICS

Method	Dose
Single wound injection	0.5% bupivacaine, 10–20 mL
Indwelling catheter	0.125% bupivacaine, 10–20 mL twice daily

Adapted from Scott DB: Acute pain management. In Cousins MJ, Bridenbaugh PI (eds): Neural Blockade in Clinical Anaesthesia and Management of Pain, ed 2. Philadelphia, J.B. Lippincott, 1988, p 866; with permission.

persistently less pressure-induced pain 48 hours and even 10 days after their surgical procedure. These effects are obviously much longer than can be attributed to the presence of local anesthetic. They postulated that perhaps the local anesthetic blockade of nociceptive impulses prevented the sensitization of the CNS that was responsible for the maintenance of postoperative pain.

It has also been reported that women who have undergone an episiotomy for vaginal delivery under epidural anesthesia may have their wound pain reduced by prior infiltration of the episiotomy site with saline alone. Kahn and Lilford[43] postulate that the improved analgesia is the result of accommodating for inflammatory edema that would normally stretch sutured tissues. "Compression within sutured tissues is reduced as absorption of the infiltrate allows the inflammatory edema to be accommodated under less pressure."

A limitation to a single dose of local anesthetic is duration. Forty years ago, Gerwig et al[34] described a technique of inserting an indwelling polyethylene catheter beneath the anterior rectus sheath of the abdominal wound. This enabled the investigators to administer procaine repeatedly in the postoperative period and resulted in a significant reduction in the amount of narcotic required for analgesia.

Although the aforementioned studies yielded encouraging results, it is worth noting that several authors using various techniques of local anesthetic wound infiltration have failed to find significant differences in pain relief, narcotic usage, or oxygen saturation.[4, 14]

In a randomized, controlled trial, Egan and associates[26] studied local wound infiltration of 2 mL/cm of wound length with 0.25% bupivacaine (n = 202) in patients undergoing elective laparotomy compared with a control group receiving saline injection (n = 213). They found no significant difference in the incidence of postoperative atalectasis between the two groups. The two groups were also similar in analgesic usage. However, the patients represented a heterogeneous group of operations, undergoing all types of abdominal surgery.

Thomas et al[102] studied wound perfusion with bupivacaine in patients undergoing elective cholecystectomy. A catheter lying between the peritoneum and muscle was used to inject 10 mL of 0.5% bupivacaine at 4-hour intervals for 48 hours postoperatively. One group received continuous infusion, and the other received 10 mL of 0.5% bupivacaine at 4-hour intervals, compared with a placebo group receiving saline infusion (n = 10 in each group). Patients received wound perfusion for 48 hours postoperatively. They found that the bupivacaine groups, both intermittent and continuous, required less postoperative analgesia than patients who received no wound perfusion. However, the saline-perfused group also had a decrease in analgesic requirements.

Levack et al,[49] in a double-blind trial, studied local wound perfusion through an indwelling catheter for 3 days postoperatively in 50 patients undergoing elective cholecystectomy or splenectomy. One group received 10 mL of 0.5% bupivacaine and the other received saline.[49] The patients' subjective assessment of pain (visual analogue pain score), was the same in both groups. However, improvement in forced vital capacity occurred only in the bupivacaine group, and opioid requirements were greater in the saline group.

The literature has shown variable results from studies of local infiltration and wound perfusion with local anesthetic agents. These differences may be due to several factors, not the least of which are the dose delivered, timing, and concentration of anesthetic. Further, the technique assumes that a significant amount of the patient's pain is due to abdominal wall or wound pain. It does not address the issue of pain arising from other potentially deeper or remote structures.

One interesting finding in several of these studies is the equivalent effectiveness of saline infiltration. This calls into question the mechanism of analgesic action. It may be that local wound infiltration acts to dilute, or remove, local pain mediators, and therefore saline is equally effective, or it may be that the benefit is due to a placebo effect.

The current literature does not consistently show improvements in pain management with the use of postoperative wound infiltration with local anesthetic agents. However, the studies that do show an improvement using these techniques found them to be simple, safe, and effective. Therefore, these techniques may be useful in selected subgroups of patients that have yet to be clearly defined.

PERIPHERAL NERVE BLOCKS

Pain in distal areas of patient extremities are often amenable to neural blockade of small nerves. Fingers and toes are supplied by digital nerves (dorsal and volar in the hand, dorsal and plantar in the foot), and these nerves are easily blocked using digital ring blocks. Wrist and ankle blocks are also relatively simple to perform. Therefore, operations involving hands or feet, whatever the method of intraoperative anesthesia, could be followed with such nerve blocks to supplement postoperative analgesia. Although standard techniques are familiar to most anesthesiologists and have enjoyed some success, alternative approaches may offer advantages.[95]

Digital nerve blocks expose the patient to the uncommon, but serious, complication of ischemia and possibly necrosis. Therefore, it is strongly recommended that epinephrine-containing solutions be avoided, and in order to minimize mechanical pressure effects of injecting solutions into confined spaces, volumes of less than 2 mL should be used on each side.

Local anesthetic blockade of the dorsal nerve of the penis can be performed to provide analgesia to the penis, permit circumcision, and provide postoperative analgesia.[44, 51, 106] There has been some dispute concerning the proper drug and dosage in order to provide a rapid onset, long duration, and minimize the peak serum concentration of local anesthetic. A mixture of lidocaine, 1 mg/kg, and bupivacaine, 0.25 mg/kg, was found to provide equally effective and prolonged analgesia as a dose of bupivacaine, 0.5 mg/kg, with significantly lower serum levels of bupivacaine.[94] Epinephrine must never be used because of the risk of ischemia. Other potential complications include hematoma and intravascular injection.

Ilioinguinal and iliohypogastric nerves can provide analgesia following herniorrhaphy. The use of 0.25 mg/kg of 0.5% bupivacaine is a common technique in pediatric surgery. Recently there has been some evidence that the simple instillation of bupivacaine into the hernia wound is as effective as ilioinguinal/iliohypogastric nerve block in providing postoperative analgesia.[15]

Another possible use for ilioinguinal nerve block is in patients who undergo cesarean section through Pfannenstiel's incision under general anesthesia. Bilateral blockade of the ilioinguinal and iliohypogastric nerves at the level of the anterior superior iliac spine produces analgesia covering the dermatome supplied by the first lumbar nerve (where Pfannenstiel's incision lies). Bunting and McConachie[12] found that postoperative analgesia was improved and less systemic analgesia was required when using this technique. It is noteworthy that while providing analgesia of the skin and deeper layers of the anterior abdominal wall, this block does not provide visceral analgesia.

Sciatic and Femoral Nerve Blocks

Smith et al[97] described a technique for continuous sciatic nerve block using an epidural catheter in the neurovascular space surrounding the sciatic nerve. A continuous infusion of 0.5% bupivacaine enabled them to provide 4 days of perioperative analgesia to a patient with a gangrenous foot.

Femoral nerve block has been used successfully to treat the pain of reconstructive knee surgery,[77, 104] and fractured femoral shafts,[105] and when combined with sciatic nerve blockade, has resulted in adequate analgesia and muscle relaxation to permit complete evaluation of an acute knee injury.[80] A single-shot femoral nerve block may be of limited applicability because complete anesthesia of the knee would require anesthetizing not only the femoral nerve but the obturator, lateral femoral cutaneous, and sciatic nerves as well. Use of the "3 in 1" technique of Winnie necessitates the use of large volumes (40–45 mL) of local anesthetic, and to reduce systemic absorption (and possible development of toxic effects), the use of epinephrine-containing solutions has been shown to be effective.[78, 114]

Continuous femoral analgesia by indwelling inguinal catheter has been reported as a successful technique for management of postsurgical lower extremity pain.[83] Advancement of a catheter in the fascial sheath of the femoral nerve to permit a continuous block of the lumbar plexus has resulted in significantly improved analgesia and lower demand for morphine in patients undergoing open knee joint surgery.[20, 21] Serpell and his colleagues[93] in a similar study found this technique to be effective and to reduce narcotic requirements, but not to result in improved analgesia (as measured by pain scores) or a lower incidence of side effects such as nausea and vomiting.

Miscellaneous Peripheral Nerve Blocks

Although the need to block some peripheral nerves may arise only infrequently, several authors have described peripheral nerve block techniques that may prove beneficial in selected patients.

Ramamurthy et al[70] were the first to describe blockade of the long thoracic nerve, which they used in an attempt to alleviate right lateral chest wall pain in a patient who had suffered a twisting, pulling injury to the muscle. Pain that was attributed to spasm of the serratus anterior muscle was completely relieved by local anesthetic blockade of the long thoracic nerve. The long thoracic nerve is a mixed sensory/motor nerve arising from the anterior branches of the C5, C6, and C7 nerve roots and usually innervates a single muscle, the serratus anterior. Subsequently, they performed this block on six more patients, all with pain below the axilla on the chest wall. Four of these patients had excellent pain relief that outlasted the duration of the local anesthetic.

Intermittent injections of bupivacaine also have been reported to be effective in the management of a scapular fracture.[9] The insertion of an epidural catheter in the region of the scapular notch facilitated repeat injections of 10 mL of bupivacaine 0.25% with 1:200,000 epinephrine. This resulted in 8 to 10 hours of good analgesia. Interestingly, the injection of radiopaque dye demonstrated the catheter to be lateral to the scapular notch, but there was dye dispersal throughout the supraspinous fossa.

Some investigators report the successful use of paravertebral blocks.[16, 25, 27] However, these blocks largely have been replaced by epidural analgesia, which is technically easier to perform.

INTERCOSTAL NERVE BLOCK

Intercostal nerve blocks can be used to provide analgesia for pain arising from the thorax or abdomen. This technique has long been known to be an effective method of pain relief.[7] It was popularized as a technique for postoperative pain relief by Moore in the 1960s and 1970s, but continues to be underused in many centers.

Crawford and Skinner[19] studied the use of intercostal blocks for provision of postoperative analgesia in patients undergoing a rib-resecting thoracoabdominal incision (for testicular cancer) and patients undergoing flank incisions (for renal surgery). By injecting the interspace of the incision and two interspaces above and below, they found a significant decrease in the amount of narcotic required postoperatively and also a reduced incidence of postoperative atelectasis (4/45 versus 10/45 patients), which they attributed to improved ventilation, although there was no measure of respiratory mechanics.

Although this was a double-blind randomized prospective study it had no specific measurement of pain, such as pain scores. Further, the authors used a large total dose of bupivacaine (about 225 mg). Use of the 0.75% concentration has fallen into disfavor because of the fear of systemic toxicity (e.g., irreversible ventricular arrhythmias).

Intercostal nerve blocks have similarly been found to provide effective analgesia and decrease narcotic requirement following lower abdominal surgery,[12, 13] flank incisions,[64] and thoracotomy.[23, 31, 42] The attenuation of postoperative decreases in pulmonary function have been found in patients undergoing cholecystectomy[71] and thoracotomy.[23, 42] However, a number of investigators have found it difficult to document any improvement in measures of pulmonary function in postoperative patients receiving intercostal blocks.[28, 33, 81] Rosenberg and his colleagues[81] compared four treatment regimens in patients undergoing upper abdominal surgery. The treatments consisted of intercostal blocks (one 15-mL injection of 0.5% bupivacaine), epidural morphine, intramuscular narcotics, or intravenous fentanyl infusion plus on-demand bolus (i.e., patient-controlled analgesia with an infusion). They found no significant differences between the groups in pain intensity scores, chest radiographic findings, or peak expiratory flow rates (which were all decreased at 2 and 24 hours postoperatively to approximately 55% of the preoperative values).

There has been some controversy based on several anatomic, radiologic, and clinical studies regarding the possibility of blocking several intercostal nerves with a single injection.[46, 57, 58, 60, 65] Although this appears to be possible, the spread of the block is probably due to local anesthetic solution tracking medially and spreading out over two to five paravertebral spaces.

The anatomic study by Nunn and Slavin[65] revealed that even a small-volume injection (3 mL) could spread over the internal aspect of the ribs for several interspaces. This led O'Kelly and Garry[66] to attempt the introduction of an indwelling catheter into the intercostal space. They obtained excellent analgesia with repeated 20-mL boluses of 0.5% bupivacaine over 4 days in a patient with multiple rib fractures.

After gaining experience with the technique in similar rib fracture patients, Murphy[61] studied this technique in elective cholecystectomy patients. Using a 16-gauge Tuohy needle at the angle of the rib (approximately 7 cm from the midline posteriorly), the needle was advanced in a standard technique for intercostal injections. He then introduced an epidural catheter 3 to 4 cm into the intercostal space, withdrawing the needle and securing the catheter in place. If difficulty was experienced with the introduction of the catheter, reinsertion was attempted with the needle angled 10 to 20 degrees toward the midline. Bupivacaine 0.5% in 20-mL boluses was administered over the first 48 hours postoperatively. Ninety-two percent (23/25) of the patients required no opiate supplementation during the first 24 hours and 76% (19/25) required none for the first 48 hours postoperatively. The mean duration of adequate analgesia was 7 hours. Interestingly, he found a significant increase in the measure of peak expiratory flow rates 30 minutes after patients received top-up doses. Also, four patients required increasing doses of bupivacaine, suggesting the development of tachyphylaxis.

Subsequently, Murphy[62] studied the spread of india ink injected via intercostally positioned catheters in cadavers. He found the ink to spread subpleurally to interspaces above and below the one cannulated, as well as to the paravertebral space.

In the ensuing years several studies have found continuous intercostal blockade to be useful,[36, 86] but there have been conflicting opinions as to the best technique for locating the extrapleural or intrapleural space, the ultimate position of the catheter, and the site of action of the local anesthetics used.

Intercostal blocks can provide excellent analgesia, and some of the conflicting results in the literature may be partially explained by the innervation of the thoracic and abdominal cavities. Noxious stimuli from the thoracic and abdominal cavities are transmitted along afferent fibers of the somatic, sympathetic, and parasympathetic divisions of the nervous system. Complete sensory blockade of thoracic and abdominal contents can be achieved only by blocking all afferent impulses from each of these three divisions of the nervous system. This is difficult to achieve with a single regional block alone. Autonomic nerve fibers are diffuse, often ill-defined, and more difficult to isolate than most somatic nerve fibers. All anesthesiologists are familiar with the patient who responds to manipulation of abdominal viscera even though they have spinal anesthesia to upper thoracic dermatomes. Similarly, we have all seen patients respond to uterine manipulation while under epidural anesthesia that is perfectly adequate for skin incision and abdominal wall relaxation. Blockade of all these nerves via celiac plexus block or vagal nerve block is technically difficult and fraught with many potential side effects.

INTERPLEURAL ANALGESIA

An alternative approach to blockade of intercostal nerves appears to be the deposition of local anesthetic into the interpleural space.

Reiestad and Stromskag[74] initially described the technique in 81 patients undergoing unilateral breast surgery, renal surgery, or cholecystectomy with a subcostal incision. Using a Tuohy needle, a lubricated glass syringe, and the loss of resistance technique, an epidural catheter was placed between the parietal and visceral pleura (Fig. 1). The use of 20 mL of 0.5% bupivacaine provided complete analgesia in 78 of the 81 patients for a mean duration of 10 hours.

This report was followed by many studies attempting to define this technique's applicability, mechanism of action, and safety. When compared with multiple intercostal blocks, interpleural block has the advantage of requiring only a single needle puncture, and the lack of sympathetic blockade, systemic hypotension, and respiratory depression appeared to be advantages when compared with epidural blockade.[109] Interpleural analgesia generated such enthusiasm that it quickly became the subject of several editorials in the anesthesia literature.[18, 50]

The effectiveness of the technique in upper abdominal surgery is well documented,[6, 11, 47, 100, 107] and it has been reportedly used with good results in the treatment of multiple rib fractures,[40, 79] herpes zoster,[96] and even reflex sympathetic dystrophy.[73] There are also several reports of successful management of chronic pain conditions.[1, 24, 72] More controversial is the usefulness of this technique in patients undergoing thoracotomy.

Interpleural Analgesia in Thoracotomy

Although McIlvaine et al[53] and Kambam et al[41] have shown this is an effective technique in children and adults undergoing thoracotomy, other investigators have not found this to be the case.

Rosenberg and his colleagues[82] studied patients undergoing tho-

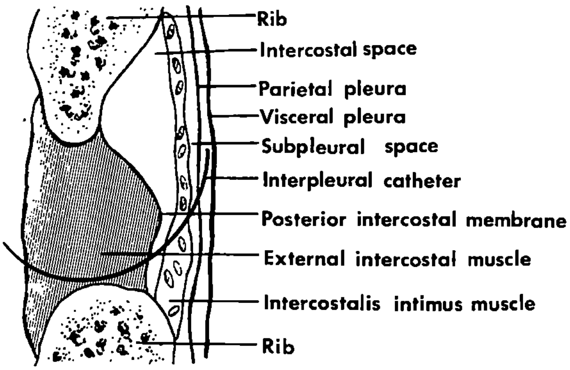


Figure 1. Cross-section of the intercostal space showing an interpleural catheter lying between the visceral and parietal pleura. (*From* Ferrante FM, Chan VWS, Arthur R, et al: Interpleural analgesia after thoracotomy. Anesth Analg 72:105–109, 1991; with permission.)

racotomy. An epidural catheter was inserted into the interpleural space under direct vision before wound closure. After a loading dose they used a continuous infusion of 0.25% bupivacaine and provided intramuscular oxycodone on request to supplement postoperative analgesia. Their patients did not achieve satisfactory analgesia with this technique, despite a wide range of plasma bupivacaine concentrations (plasma bupivacaine concentrations increased over the course of the 2 days of continuous infusion to a mean of 2.29 μg/mL). An interesting aspect of this study was the measurement of bupivacaine concentration in the fluid drained from the thoracostomy tubes. In patients requiring thoracostomy tubes connected to suction (e.g., lobectomy, exploratory thoractomy), the bupivacaine concentration in the pleural drainage fluid was very high (levels of 447–1725 μg/mL). If a substantial amount of the local anesthetic was drained out of the chest tubes, it is not surprising that the technique was ineffective.

Rosenberg's group[87] then went on to evaluate the effectiveness of interpleural bupivacaine boluses with temporary clamping of the chest drainge tubes. Although this resulted in significantly less bupivacaine being found in the pleural drainage fluid, the analgesia provided was not effective enough to result in a decrease in these patients' overall postoperative narcotic analgesic requirement.

More recently, Ferrante et al[30] compared the use of one catheter (with catheter tip aligned paravertebrally) versus two interpleural catheters (with second catheter aligned laterally). This study also confirmed the loss of a significant amount of injected bupivacaine (30%–40% of administered doses) via the thoracostomy drainage tubes, but did find significantly enhanced analgesia using a double-catheter technique in post-thoracotomy patients.

The mechanism of interpleural analgesia is believed to be primarily due to the diffusion of local anesthetic back through the parietal pleura and intercostalis intimus muscle to reach multiple intercostal nerves. Several clinical studies have raised the possibility that this technique may involve splanchnic nerves, sympathetic chain ganglia, or other visceral neural structures. Laboratory evidence in a dog model using somatosensory evoked potentials confirmed that interpleural bupivacaine can produce intercostal nerve block.[76]

If the local anesthetics can diffuse readily through pleura and intercostal muscles, then it is possible that they may spread to involve the thoracic sympathetic chain. The study by Reiestad et al[73] in which seven patients with reflex sympathetic dystrophy were treated with interpleural local anesthetic supports this mechanism. The technique involved keeping patients in the lateral ducubitus position with a slight head down tilt of 20 degrees, and administration of 30 mL of 0.5% bupivacaine with epinephrine, 5 μg/mL. This resulted in the development of a profound sympathetic block of the ipsilateral upper extremity in all seven patients.

That splanchnic nerves also may be blocked by local anesthetic deposited in the interpleural space seems to be confirmed by several series that report the successful treatment of pain due to carcinoma of the pancreas[24] and chronic pancreatitis pain.[1, 72] According to most standard anatomy texts, the splanchnic nerves arise from the roots of T5 to T12 or L1. Pancreatic pain is transmitted along afferent fibers from the pancreas to the splanchnic nerves and also by the lower intercostal nerves, which innervate the peritoneum. Thus, the excellent analgesia resulting from the interpleural catheter in these series seems to indicate that both splanchnic and intercostal blockade can be achieved with this technique.

Using contrast medium and computerized tomography, Stromskag et al[99] demonstrated that interpleurally injected local anesthetic spreads to the roots of intercostal, splanchnic, and sympathetic nerves, depending on patient position. Interestingly, this group did not find contrast medium spreading to either the epidural or paravertebral spaces. Animal models of the spread of intrapleurally injected solutions suggest that accumulation in the paravertebral area is possible.[55]

The optimal dosage of local anesthetic has not been clearly defined. Although adequate analgesia has been reported with as little as 8 mL of 0.5% bupivacaine,[24] other investigators have required considerably larger doses (30 mL of 0.5% bupivacaine[81]) to achieve satisfactory analgesia. Most authors appear to use an initial bolus dose of 20 mL of 0.5% bupivacaine with good results. In a study comparing 0.25%, 0.375%, and 0.5% bupivacaine,[100] equal degrees of analgesia were achieved, with an increased duration of effect (4.3, 6, 7.7 hours, respectively) being attained by the increase in concentration.

Does the addition of epinephrine to the local anesthetic minimize the potential complication of systemic toxicity? There is now evidence that this is probably true. In a study using bupivacaine, 2.5 mg/kg, with or without epinephrine, 5 μg/mL, peak plasma concentrations were lower in the epinephrine group (mean, 2.57 versus 3.22 μg/mL) and the time to maximum concentration was delayed (mean, 25 versus 15 minutes).[35] Using a double catheter technique, Ferrante et al[30] found that the addition of epinephrine 1:200,000 to bupivacaine 0.5% appeared to result in lower peak plasma concentrations (0.21 μg/mL with epinephrine versus 0.79 μg/mL without epinephrine) although this did not reach the level of statistical significance.

Technique

Most investigators have used the technique originally described by Reiestad for cannulation of the interpleural space using a Tuohy needle, lubricated glass syringe, and epidural catheter, or they have the catheter positioned intrathoracically by the surgeon before closure of the thoracic cavity. Recently several modifications have been suggested as improvements in technique.[89, 98] Squier et al[98] (and a modification by Ben-David) described a "hanging drop" technique that entails removing the needle stylet and attaching a syringe to the hub of the Tuohy needle. The syringe is then filled with several milliliters of saline, and the needle is advanced. Proper placement occurs as the column of fluid falls away as the saline is pulled into the interpleural space. A novel approach for identification of the interpleural space has been suggested by Sydow and Haindl.[101] Their technique involves a latex balloon that collapses under the negative pressure of the pleural cavity. This technique has been used successfully in a series of 71 patients.

Potential complications of this technique are predictable. The needling of the thorax can cause pneumothorax, and although most of the aforementioned studies did not find this to be a clinically significant problem, at least one author[10] found that 4 of 21 patients developed pneumothorax. The possible rapid vascular absorption of local anesthetic solution resulting in a toxic blood level has been investigated by several groups.[45, 56, 92] Seltzer found that maximal individual bupivacaine plasma concentrations in 11 patients were reached between 10 and 30 minutes after injection and ranged from 1.1 to 3.3 μg/mL (toxicity occurs with levels above 5 μg/mL). One patient developed seizures and had a plasma bupivacaine level of 4.9 μg/mL. This patient had a small collection of pleural fluid, and the authors postulate that the pleura was highly inflammed, and this allowed for rapid absorption of the local anesthetic. This raises the unanswered question of the use of interpleural anesthetics in patients with underlying pulmonary pathology. It was originally reported[74] that a patient with pulmonary fibrosis due to previous tuberculosis failed to obtain analgesia with this technique.

Relative contraindications to the use of this technique might include pleural fibrosis or adhesions, effusions plus the usual contraindications to regional anesthesia of local infection, and bleeding diathesis. It is noteworthy that the technique has been used successfully in patients with cystic fibrosis[11] and has been found to improve postoperative pulmonary function.[32]

BRACHIAL PLEXUS BLOCK

As with other regional anesthetic techniques, single-shot brachial plexus blocks have been used to provide analgesia with success following various surgical procedures.[63, 103] In women undergoing modified radical mastectomy, Fassoulaki[29] found improved postoperative analgesia as defined by the delayed request for and decreased total requirement of systemic analgesics. In this study the surgeon infiltrated the brachial plexus and several intercostal spaces under direct vision using an infraclavicular approach, which the author proposed as a far more effective technique for blocking the brachial plexus than an axillary or interscalene block. As well as analgesia and muscle relaxation, the accompanying sympathetic block can reduce the vasospasm and edema associated with traumatic injury to an extremity. The effective use of brachial plexus block in the management of upper extremity fractures and dislocations also has been reported.[38]

Pediatric patients undergoing upper extremity surgery under general anesthesia have been shown to have excellent initial postoperative analgesia if they receive a brachial plexus block before emergence. McNeely et al[53] found superior analgesia as measured by pain score and a decreased narcotic requirement for the first 6 hours postoperatively. Using a "parascalene approach" they had a high success rate for establishing a block.

A potentially useful technique for providing continuous upper extremity analgesia is that of continuous local anesthetic infusion around the brachial plexus. As early as 1946 a technique involving the fixation of a blunt-tipped needle (by means of a cork and adhesive tape), followed by continuous infusion of 1% procaine, was described as successfully providing anesthesia for surgical procedures of varying lengths.[3] As equipment and technology advanced over the ensuing years, the introduction of plastic catheters was followed by the description by DeKrey et al[22] of continuous brachial plexus anesthesia via cannulation of the brachial plexus sheath. Winnie et al[114] described an interscalene approach that consists of threading a plastic catheter over a needle and inserting the two together. Once appropriate paresthesia has been elicited, the needle serves as a guide, whereupon the outer catheter is advanced a short distance into the fascial sheath. Difficulties in proper placement and maintenance of this placement has led investigators to attempt alternate techniques. A number of approaches have since been described,[39, 91, 110, 111] including the axillary approach, the supraclavicular approach, and the infraclavicular approach. Also modifications of needle and catheter placement, such as the Seldinger technique, have been reported as both easy and effective.[84]

These techniques are based on the premise that a single injection of anesthetic solution into the fascial sheath containing the neurovascular bundle will adequately spread to block components of all major brachial plexus nerves. Some degree of controversy arose when Thompson et al[103] described the compartmentalization of the neurovascular bundle, with compartments being formed by septa that extend inward from the sheath. It was postulated that septa may block the spread of local anesthetic and necessitate multiple injections for effective blockade. This issue is the subject of an excellent review by Selander,[90] and the success of the continuous catheter techniques cited seems to corroborate the opinion that single-compartment injections are very successful and that the perivascular septa of the axillary sheath seem to be functionally unimportant.

Although as with other regional techniques, prolonging the duration of analgesia is of prime importance, an interesting study by Heath et al[37] may lead to improving the onset of analgesia. By warming the local anesthetic solutions to 37°C, this group was able to significantly speed the onset of sensory blockade in patients undergoing subclavian brachial plexus blocks with 0.5% bupivacaine plus 1:200,000 epinephrine.

The development of microvascular and reconstructive hand surgery has lead to a demand for prolonged regional anesthesia. Techniques for catheterization of the brachial plexus can offer the physician an additional option for the treatment of acute pain in the upper extremity.

FUTURE DEVELOPMENTS

There is evidence that the CNS displays a capacity for neural plasticity in response to noxious somatosensory inputs. The data suggest that noxious stimuli or injury may produce long-term changes in CNS function that are experienced as pain long after the offending stimulus has been removed.[5, 54, 112] The "injury barrage" generated in central cells appears to have a sensitizing effect. Subsequent noxious inputs may be perceived to be more painful than they would otherwise have been. It has been hypothesized that a block of the sensory pathways prior to surgical incision would eliminate this sensitizing effect and result in reduced postoperative pain. Future research in this area may assist in reducing acute pain in the elective surgical patient.

It is hoped that new local anesthetic drugs with less toxicity and longer durations will become available. Ropivicaine is a member of the same chemical family as bupivacaine, and early studies have shown it to be less cardiotoxic than bupivacaine, with a similar pharmacokinetic profile.[2, 75] Ongoing research will soon define this new agent's place in pain management practice. The possibility of agents that selectively block sensory neural fibers and thus avoid the often accompanying undesired motor blockade is also an area of ongoing research.

SUMMARY

The past decade has seen a renewed interest in acute pain management as the development of epidural opioids and new technologies for the delivery of systemic analgesics (e.g., patient-controlled analgesia) has led to the creation of the anesthesiology based acute pain service in many hospitals. The availability of physicians familiar with the pharmacology and physiology of local anesthetics and acute pain has resulted in advances in the use of regional anesthesia techniques in the treatment of acute pain. The role of local anesthetic blocks as supplements to systemic analgesic administration is well established, and future studies are needed to confirm the reduction of pain-related morbidity and mortality.

References

1. Ahlburg P, Noreng M, Molgard J: Treatment of pancreatic pain with interpleural bupivacaine: An open trial. Acta Anaesthesiol Scand 34:156–157, 1990
2. Akerman B, Hellenberg I, Trossvik C: Preliminary evaluation of the local anaesthetic properties of the amino amide agent ropivicaine [LEA 103]. Acta Anaesthesiol Scand 32:571–578, 1988

3. Ansbro FP: A method of continuous brachial plexus block. Am J Surg 71:716–722, 1946
4. Aull L, Woodward ER, Rout RW, et al: Analgesia and postoperative hypoxemia after gastric partition with and without bupivacaine wound infiltration. Can J Anaesth 37:S53, 1990
5. Bach S, Noreng MF, Tjellden NU: Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 33:297–301, 1988
6. Baker PA, Schroeder D: Interpleural bupivacaine for postoperative pain during lactation. Anesth Analg 69:400–402, 1989
7. Bartlett RW: Bilateral intercostal nerve block for upper abdominal surgery. Surg Gynecol Obstet 71:194–197, 1940
8. Blades B, Ford WB: A method for control of postoperative pain. Surg Gynecol Obstet 91:524–526, 1950
9. Breen TW, Haigh JD: Continuous suprascapular nerve block for analgesia of scapular fracture. Can J Anaesth 37:786–788, 1990
10. Brismar B, Pettersson N, Tokics L, et al: Postoperative analgesia with intrapleural administration of bupivacaine-adrenaline. Acta Anaesthesiol Scand 31:515–520, 1987
11. Bruce DL, Gerken MV, Lyon GD: Postcholecystectomy pain relief by intrapleural bupivacaine in patients with cystic fibrosis. Anesth Analg 66:1187–1189, 1987
12. Bunting P, McConachie I: Ilioinguinal nerve blockade for analgesia after caesarean section. Br J Anaesth 61:773–775, 1988
13. Bunting P, McGeachie JF: Intercostal nerve blockade producing analgesia after appendectomy. Br J Anaesth 61:169–172, 1988
14. Cameron AEP, Cross FW: Pain and mobility after inguinal herniorrhaphy: Ineffectiveness of subcutaneous bupivacaine. Br J Surg 72:68–69, 1985
15. Casey W, Rice L, Hannallah R: Comparison of postoperative analgesia: Bupivacaine by instillation vs ilioinguinal/iliohypogastric nerve block. Can J Anaesth 36:S155, 1989
16. Conacher ID, Kokri M: Postoperative paravertebral blocks for thoracic surgery: A radiologic appraisal. Br J Anaesth 59:155–161, 1987
17. Cousins MJ, Bridenbaugh PI: Neural Blockade in Clinical Anaesthesia and the Management of Pain, ed 2. Philadelphia, J.B. Lippincott, 1988
18. Covino BG: Interpleural regional analgesia. Anesth Analg 67:427–429, 1988
19. Crawford ED, Skinner DG: Intercostal nerve block with thoracoabdominal and flank incisions. Urology 19:25–28, 1982
20. Dahl JB, Christiansen CL, Daugaard JJ, et al: Continuous blockade of the lumbar plexus after knee surgery-postoperative analgesia and bupivacaine plasma concentrations. Anaesthesia 43:1015–1018, 1988
21. Dahl MR, Dasta JF, Zuelzer W, et al: Lidocaine local anesthesia for arthroscopic knee surgery. Anesth Analg 71:670–674, 1990
22. DeKrey JA, Schroeder CF, Buechel DR: Continuous brachial plexus block. Anesthesiology 30:332, 1969
23. Delilkan AE, Lee CK, Yong NK, et al: Post-operative local analgesia for thoracotomy with direct bupivacaine intercostal blocks. Anaesthesia 28:561–567, 1973
24. Duranni Z, Winnie AP, Ikuta P: Interpleural catheter analgesia for pancreatic pain. Anesth Analg 67:479–481, 1988
25. Eason MJ, Wyatt R: Paravertebral thoracic block—A reappraisal. Anaesthesia 34:638–642, 1979
26. Egan TM, Herman SJ, Doucette EJ, et al: A randomized, controlled trial to determine the effectiveness of fascial infiltration of bupivacaine in preventing respiratory complications after elective abdominal surgery. Surgery 104:734–740, 1988
27. Eng J, Sabanathan S: Site of action of continuous extrapleural intercostal nerve block. Ann Thorac Surg 51:387–389, 1991
28. Engberg G, Wilklund L: Pulmonary complications after upper abdominal surgery: Their prevention with intercostal blocks. Acta Anaesthesiol Scand 32:1–9, 1988
29. Fassoulaki A: Brachial plexus block for pain relief after modified radical mastectomy. Anesth Analg 61:986–987, 1982
30. Ferrante FM, Chan VWS, Arthur R, et al: Interpleural analgesia after thoracotomy. Anesth Analg 72:105–109, 1991

31. Fleming WH, Sarafian LB: Kindness pays dividends: The medical benefits of intercostal nerve block following thoracotomy. J Thorac Cardiovasc Surg 74:273–274, 1977
32. Frenette L, Boudreault D, Guay J: Interpleural analgesia improves pulmonary function after cholecystectomy. Can J Anaesth 38:71–74, 1991
33. Galway JE, Caves PK, Dundee JW: Effect of intercostal nerve blockade during operation on lung function and the relief of pain following thoracotomy. Br J Anaesth 47:730–735, 1975
34. Gerwig WH, Thompson CW, Blades B: Pain control following upper abdominal operations. Arch Surg 62:678–682, 1951
35. Gin T, Chan K, Kan AF, et al: Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. Br J Anaesth 64:662–666, 1990
36. Graziotti PJ, Smith GB: Multiple rib fractures and head injury—An indication for intercostal catheterisation and infusion of local anaesthetics. Anaesthesia 43:964–966, 1988
37. Heath PJ, Brownlie GS, Herrick MJ: Latency of brachial plexus block. Anaesthesia 45:297–301, 1990
38. Heffington CA, Thompson RC: The use of interscalene block anaesthesia for manipulative reduction of fractures and dislocations of the upper extremities. J Bone Joint Surg Br 55:83–86, 1973
39. Hempel V, van FM, Baumgartner E: A longitudinal supraclavicular approach to the brachial plexus for the insertion of plastic cannulas. Anesth Analg 60:352–355, 1981
40. Hudes ET: Continuous infusion interpleural analgesia for multiple fractured ribs. Can J Anaesth 37:705, 1990
41. Kambam JR, Handte RE, Flanagan J, et al: Intrapleural anesthesia for post thoracotomy pain relief. Anesth Analg 67:S90, 1987
42. Kaplan JA, Miller ED, Gallagher Jr EG: Postoperative analgesia for thoracotomy patients. Anesth Analg 54:773–777, 1975
43. Khan GQ, Lilford RJ: Wound pain may be reduced by prior infiltration of the episiotomy site after delivery under epidural analgesia. Br J Obstet Gynaecol 94:341–344, 1987
44. Kirya C, Werhmann MW: Neonatal circumcision and penile dorsal nerve block—A painless procedure. J Pediatr 92:998–1000, 1978
45. Kliffer AP, Wiesel S, Lubenskyi W, et al: Interpleural bupivacaine does not lead to elevated plasma levels in the elderly. Anesth Analg 72:S140, 1991
46. Krino K, Lindell K: Intercostal nerve blockade. Br J Anaesth 58:250, 1986
47. Laurito CE, Kirz LI, VadeBoncouer TR, et al: Continuous infusion of interpleural bupivacaine maintains effective analgesia after cholecystectomy. Anesth Analg 72:516–521, 1991
48. Lee VC: Non-narcotic modalities for the management of acute pain. Crit Care Clin 6:451–481, 1990
49. Levack ID, Holmes JD, Robertson GS: Abdominal wound perfusion for the relief of postoperative pain. Br J Anaesth 58:615–619, 1986
50. Lewis GW: Interpleural block [editorial]. Can J Anaesth 36:103–105, 1989
51. Lunn JW: Postoperative pain after circumcision. Anaesthesia 34:552–554, 1979
52. McIlvaine WB, Knox RF, Fennessey PV, et al: Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 69:261–264, 1988
53. McNeely JK, Hoffman GM, Eckert JE: Postoperative pain relief in children from the parascalene injection technique. Reg Anesth 16:20–22, 1991
54. McQuay HJ, Carrol D, Moore RA: Post-operative orthopedic pain—The effect of opiate premedication and local anaesthetic blocks. Pain 33:291–295, 1988
55. Miserocchi G, Pistolesi M, Miniati M, et al: Pleural liquid pressure gradients and intrapleural distribution of injected bolus. J Appl Physiol 56:526–532, 1984
56. Mogg GA, Triggs EJ, Ismail Z, et al: Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy. Br J Anaesth 64:657–661, 1990
57. Moore DC: Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. Br J Anaesth 47:284, 1975
58. Moore DC: Intercostal nerve block: Spread of india ink injected to the rib's costal groove. Br J Anaesth 53:325–329, 1981

59. Moss G, Regal ME, Lichtig L: Reducing postoperative pain, narcotics, and length of hospitalization. Surgery 99:206–210, 1986
60. Mowbray A, Wong KKS: Low volume intercostal injection. A comparative study in patients and cadavers. Anaesthesia 43:633–634, 1988
61. Murphy DF: Continuous intercostal nerve blockade for pain relief following cholecystectomy. Br J Anaesth 55:521–523, 1983
62. Murphy DF: Continuous intercostal nerve blockade: An anatomical study to elucidate its mode of action. Br J Anaesth 56:627–630, 1984
63. Neill RS: Postoperative analgesia following brachial plexus block. Br J Anaesth 50:379–382, 1978
64. Noller DW, Gillenwater JY, Howards SS, et al: Intercostal nerve block with flank incision. J Urol 117:759–761, 1977
65. Nunn JF, Slavin G: Posterior intercostal nerve block for pain relief after cholecytectomy: Anatomical basis and efficacy. Br J Anaesth 52:253–259, 1980
66. O'Kelly E, Garry B: Continuous pain relief for multiple fractured ribs. Br J Anaesth 53:989–991, 1981
67. Owen H, Galloway DJ, Mitchell KG: Analgesia by wound infiltration after surgical excision of benign breast lumps. Ann R Coll Surg Engl 67:114–115, 1985
68. Partridge BL, Stabile BE: The effects of incisional bupivacaine on postoperative narcotic requirements, oxygen saturation and length of stay in the post-anesthesia care unit. Acta Anaesthesiol Scand 34:486–491, 1990
69. Patel JM, Lanzafame RJ, Williams JS, et al: The effect of incisional infiltration of bupivacaine hydrochloride upon pulmonary functions, atalectasis and narcotic need following elective cholecystectomy. Surg Gynecol Obstet 28:338–340, 1983
70. Ramamurthy S, Hickey R, Maytorena A, et al: Long thoracic nerve block. Anesth Analg 71:197–199, 1990
71. Rawal N, Sjostrand UH, Dahlstrom B, et al: Epidural morphine for postoperative pain relief: A comparative study with intramuscular narcotic and intercostal nerve block. Anesth Analg 61:93–98, 1982
72. Reiestad F, McIlvaine WB, Kvalheim L, et al: Successful treatmentoof chronic pancreatitis with interpleural analgesia. Can J Anaesth 36:613–716, 1989
73. Reiestad F, McIlvaine WB, Kvalheim L, et al: Interpleural analgesia in treatment of upper extremity reflex sympathetic dystrophy. Anesth Analg 69:671–673, 1989
74. Reiestad F, Stromskag KE: Interpleural catheter in the management of postoperative pain: A preliminary report. Reg Anesth 11:89–91, 1986
75. Reiz S, Nath SW: Cardiotoxicity of LEA 103—A new amide local anaesthetic agent. Acta Anaesthesiol Scand 33:93–98, 1989
76. Riegler FX, Vade Boncouer TR, Pelligrino DA: Interpleural anesthetics in the dog: Differential somatic neural blockade. Anesthesiology 71:744–750, 1989
77. Ringrose NH, Cross MJ: Femoral nerve block in knee joint surgery. Am J Sports Med 12:398–402, 1984
78. Robison C, Ray DC, McKeown DW, et al: Effect of adrenaline on plasma concentrations of bupivacaine following lower limb nerve block. Br J Anaesth 66:228–231, 1991
79. Rocco A, Reiestad F, Gudman J, et al: Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. Preliminary report. Reg Anesth 12:10–14, 1987
80. Rooks M, Fleming LL: Evaluation of acute knee injuries with sciatic/femoral nerve blocks. Clin Orthop 179:185–188, 1982
81. Rosenberg PH, Heino A, Schenin B: Comparison of intramuscular analgesia, intercostal block, epidural morphine and on-demand-iv fentanyl in the control of pain after upper abdominal surgery. Acta Anaesthesiol Scand 28:603–606, 1984
82. Rosenberg PH, Scheinin B, Lepantalo MJA, et al: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 67:811–813, 1987
83. Rosenblatt RM: Continuous femoral anesthesia for lower extremity surgery. Anesth Analg 59:631–632, 1980
84. Rosenblatt RM, Cress JC: Modified Seldinger technique for continuous interscalene brachial plexus block. Reg Anesth 6:82–84, 1981
85. Rung GW, Marshalk WK: Nerve blocks in the critical care enviornment. Crit Care Clin 6:343–367, 1990

86. Safran D, Kuhlman G, Orhant EE, et al: Continuous intercostal blockade with lidocaine after thoracic surgery: Clinical and pharmacokinetic study. Anesth Analg 70:345–349, 1990
87. Scheinin B, Lindgren L, Rosenberg PH: Treatment of post-thoracotomy pain with intermittent instillations of intrapleural bupivacaine. Acta Anaesthesiol Scand 33:156–159, 1989
88. Scott DB: Acute pain management. *In* Cousins MJ, Bridenbaugh PI (eds.): Neural Blockade in Clinical Anaesthesia and Management of Pain, ed 2. Philadelphia, J.B. Lippincott, 1988, pp 861–883
89. Scott PV: Interpleural regional analgesia: Dectection of the interpleural space by saline infusion. Br J Anaesth 66:131–133, 1991
90. Selander D: Axillary plexus block: Parasthetic or perivascular. Anesthesiology 66:726–728, 1987
91. Selander D: Catheter technique in axillary plexus block. Acta Anaesthesiol Scand 21:324–329, 1977
92. Seltzer JL, Larijani GE, Goldberg M, et al: Intrapleural bupivacaine—A kinetic and dynamic evaluation. Anesthesiology 67:798–800, 1987
93. Serpell MG, Millar FA, Thomson MF: Comparison of lumbar plexus block versus conventional opiod analgesia after total knee replacement. Anaesthesia 46:275–277, 1991
94. Sfez M, Le Mapihan Y, Mazoit X, et al: Local anesthetic serum concentration after penile nerve block in children. Anesth Analg 71:423–426, 1990
95. Sharrock NE, Waller JF, Fierro LE: Midtarsal block for surgery of the forefoot. Br J Anaesth 58:37–40, 1986
96. Sihota MK, Ikuta PT, Holmblad BR, et al: Successful pain management of chronic pancreatitis and post herpetic neuralgia with intrapleural technique. Reg Anaesth 13(suppl):40, 1988
97. Smith BE, Fischer HBJ, Scott PV: Continuous sciatic nerve block. Anaesthesia 39:155–157, 1984
98. Squier RC, Morrow JS, Roman R: Hanging-drop technique for intrapleural analgesia. Anesthesiology 70:882, 1989
99. Stromskag KE, Hauge O, Steen PA: Distribution of local anaesthetics injected into the interpleural space, studied by computerized tomography. Acta Anaesthesiol Scand 34:323–326, 1990
100. Stromskag KE, Reistad F, Holmqvist ELO, et al: Intrapleural administration of 0.25%, 0.375%. and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 67:430–434, 1988
101. Sydow FW, Haindl H: A new method of achieving pleural blockade. Anaesthetist 39:280–282, 1990
102. Thomas DFM, Lambert WG, Williams KL: The direct perfusion of surgical wounds with local anaesthetic solution: An approach to postoperative pain? Ann R Coll Surg Engl 65:226–229, 1983
103. Thompson AM, Newman RJ, Semple JC: Brachial plexus anaesthesia for upper limb surgery: A review of eight years experience. Br J Hand Surg 13:195–198, 1988
104. Tierney E, Lewis G, Hurtig JB, et al: Femoral nerve block with bupivacaine 0.25% for postoperative analgesia after open knee surgery. Can J Anaesth 34:455–458, 1987
105. Tondare AS, Nadkarni AV: Femoral nerve block for fractured shaft of femur. Can Anaesth Soc J 29:270–271, 1982
106. Tree-Trakarn T, Pirayavaraporn S: Postoperative pain relief for circumcision in children: Comparison among morphine, nerve block, and topical analgesia. Anesthesiology 62:519–522, 1985
107. Trivedi NS, Robalino J, Shevde K: Interpleural block: A new technique for regional anaethesia during percutaneous nephrostomy and nephrolithotomy. Can J Anaesth 37:479–481, 1990
108. Tverskoy M, Cozacov C, Ayache M, et al: Postoperative pain after inguinal herniorrhaphy with different types of anaesthesia. Anesth Analg 70:29–35, 1990
109. van Kleef JW, Burm AGL, Vletter AA: Single-dose interpleural versus intercostal blockade: Nerve block characteristics and plasma concentration profiles after administration of 0.5% bupivacaine with epinephrine. Anesth Analg 70:484–488, 1990

110. Vatashky E, Aronson HB: Continuous interscalene brachial plexus block for surgical operations on the hand. Anesthesiology 53:356, 1980
111. Vongvises P, Panijayanoud T: A parascalene technique of brachial plexus anesthesia. Anesth Analg 58:267–273, 1979
112. Wall PD: The prevention of postoperative pain. Pain 33:289–290, 1988
113. Wildsmith JAW: Developments in local anaesthetic drugs and techniques for pain relief. Br J Anaesth 63:159–164, 1989
114. Winnie AP, Ramamurthy S, Durrani Z: The inguinal paravascular technic of lumbar plexus anesthesia: "The 3-in-1 block." Anesth Analg 52:989–996, 1973

Address reprint requests to

Larry Panos, MD
Acute Pain Service
Department of Anaesthesia
Toronto General Hospital
Ste 1404, 45 Carlton Street
Toronto, Ontario
Canada M5B 2H9

CURRENT CONCEPTS IN ACUTE PAIN CONTROL 0889–8537/92 $0.00 + .20

PEDIATRIC ACUTE PAIN CONTROL

Desmond G. Spence, MB, FRCPC, and
Jane M. Henderson, MD, FRCPC

All children, even the very smallest neonate, have the capacity to experience pain.[3] Until quite recently there was still a reluctance on the part of those who care for children to administer analgesics.[10, 35, 75, 107] Now that it is generally accepted that children can and do experience pain, the problems remaining are to determine ways of assessing the degree of pain and the best method of treatment.

PAIN ASSESSMENT

The degree of pain may be communicated by self-report, behavioral responses, or changes in physiologic or metabolic parameters.

Self-Report

In adults, a visual analogue scale has become the standard against which other methods of pain assessment are measured. Simple visual analogue scales have been validated and shown to be reliable in children over 5 years of age.[81] Unfortunately, self-report cannot be used by preverbal children, and in older children, may be limited by their vocabulary and experience. Various tools have been designed to graphically represent the visual analogue scale, e.g., the Oucher[10] and the Analog Chromatic Continuous Scale.[48] The Oucher is a display with a

---

From the Department of Anaesthesia, Montreal Children's Hospital, and McGill University, Montreal, Quebec, Canada

numerical scale on the left for older children and on the right photographs of a 4-year-old with varying facial expressions. The Analog Chromatic Continuous Scale has a progressive color scale from pink to red, the darker color representing greater pain. The patient positions a slide to correspond with the degree of discomfort and this level can be read on a 10-cm scale on the opposite side. Both models have been validated for children between 3 and 7 years old but have been criticized, the Oucher because the photographs are only of a caucasian child and are fairly age specific, and the Analog Chromatic Continuous Scale because children may have different personal biases relating color intensity to pain. Pain questionnaires also have been developed for children, e.g., the Children's Comprehensive Pain Questionnaire.[82]

Behavioral Tools

Behavioral tools are based on the assumption that the perception of pain results in specific responses, e.g., certain movements, crying, facial expression, and complex behavioral patterns, which can be recorded and interpreted by an observer. The Children's Hospital of Eastern Ontario Pain Scale[84] was found to be valid and reliable for assessing pain in the recovery room in postoperative circumcision patients aged 3 to 7 years old. Behavior may be inhibited by pain from an incision, by medication, and through a desire to appear in control, and there have been questions about the reliability of this tool outside the recovery room. Behavioral responses to pain that have been studied in infants include the interpretation of general motor responses, vocalizations,[125] facial expressions,[49] and torso and limb positions,[83] but from birth, infants can have marked individual differences in behavior when painfully stimulated.

Physiologic Tools

Measurable responses to pain include change in heart rate, respiratory rate, palm sweating, stress response hormones, transcutaneous PO_2 oxygen saturation, and endorphin concentrations. Although there are a number of studies showing a relationship between physiologic response and other pain measures, it can be difficult to differentiate those changes due to anxiety from those due to pain.

In general, pain in children under 3 years of age is more accurately quantified by behavior or changes in physiologic or metabolic parameters. Self-report techniques of assessing pain are mainly of value in patients aged 3 years or older and include the use of a simple visual analogue scale or one of the various modifications. As children approach adolescence, simple visual analogue scales and pain questionnaires become more valid and reliable. The reader is referred to an excellent review article by McGrath[83] that discusses the different methods of assessment in detail.

TREATMENT

The primary reason to treat or prevent pain in children is humanitarian. This is even more important in small children who rely completely on their parents or caregivers for their well-being. There are secondary reasons to ensure that patients are comfortable. The body responds to pain and injury by producing metabolic, hormonal, and hemodynamic changes.[128] This may have profound negative effects, resulting in protein breakdown, insulin resistance, and lipolysis.[2] Anand et al[2] examined the stress response in babies anesthetized with either nitrous oxide or nitrous oxide plus fentanyl. Compared with the fentanyl group, the nonfentanyl group had a substantial stress response and more circulatory and metabolic complications postoperatively. None of the infants in the study showed any physiologic evidence of inadequate anesthesia.

Important nonpharmacologic techniques of treating acute pain include the teaching of coping mechanisms, e.g., hypnosis and transcutaneous electrical nerve stimulation, which are outside the scope of this article, but the reader is referred to articles on hypnosis and transcutaneous electrical nerve stimulation.[36, 64, 93, 94, 113, 124, 137, 138]

The pharmacologic treatment of acute pediatric pain includes the management of procedural pain, the administration of parenteral analgesics, and performance of regional blocks. Table 1 summarizes indications and suggested analgesic therapy for various etiologies and locations of pain.

Pain Associated with Procedures

Examples of painful procedures that may be encountered in pediatric practice include venipuncture, lumbar puncture, bone marrow aspiration, cardiac catheterization, and the treatment of fractures, including closed reduction or application of traction.

Children are significantly distressed by venipuncture[38] and often see a needlestick as the most threatening part of a hospital visit. Techniques to ameliorate the anxiety and discomfort of needle infiltration include the use of local anesthesia or nitrous oxide.

Until relatively recently the only way a local anesthetic could provide analgesia to intact dermis was by needle infiltration. To a child, the fact that one injection will lessen the pain of a subsequent injection does not help to alleviate anxiety.[115] A eutectic mixture of local anesthetic (EMLA) cream, applied topically, penetrates intact skin and so is painless. When applied at least 60 minutes beforehand, it has been shown to diminish the pain associated with venous cannulation.[51, 53, 74, 76] There are some disadvantages with its use: (1) the 60-minute delay to full efficacy following application; (2) the need to reapply EMLA at a second site with a subsequent delay if venipuncture fails at the first site; and (3) a possible risk of methemoglobinemia secondary to absorp-

Table 1. INDICATIONS AND SUGGESTED ANALGESIC THERAPY FOR VARIOUS SOURCES AND LOCATIONS OF PAIN

Type and/or Site of Acute Pain	Examples of Analgesic Therapy
Procedural	
Venipuncture	EMLA cream, N_2O/O_2
Lumbar puncture	EMLA cream, N_2O/O_2
Bone marrow biopsy	EMLA cream, N_2O/O_2, oral/IV benzodiazepines and opioids
Cardiac catheterization	EMLA cream, ketamine
Upper limb fracture reduction	Brachial plexus block
Femoral fracture reduction/traction	Femoral nerve block
Preinduction	EMLA cream, N_2O/O_2, nasal sufentanil, oral transmucosal fentanyl citrate
Intraoperative	
Generalized	Parenteral, i.e., IV opioids, nonsteroidal anti-inflammatory drugs, PCA
Head and neck	Cervical plexus block
Upper limb	Brachial plexus block, wrist block
Thorax and upper abdomen	Intercostal nerve blocks, epidural (thoracic or lumbar), interpleural bupivacaine
Lower abdomen and genital	Epidural (lumbar or caudal), ilioinguinal/iliohypogastric, or penile nerve blocks
Lower limb	Epidural (lumbar or caudal), lumbar plexus, femoral, or sciatic nerve blocks
Sickle cell disease (vaso-occlusive crisis)	Codeine, IV opioids, PCA

tion of the prilocaine component of the EMLA.[61] One other disadvantage that also applies to subcutaneous infiltration of lidocaine is the failure to improve patient cooperation even when the venipuncture site is made analgesic.[115] Nevertheless, pain-free venipuncture from the use of EMLA may be an important first step toward a painless hospital experience.

Nitrous oxide, administered in concentrations of 50% to 70% in oxygen for 3 minutes has been shown to decrease both pain and anxiety in children undergoing venous cannulation.[58] More than one attempt at venipuncture in different locations may be made without the need to "reapply" the analgesic. Nitrous oxide has also been used outside the operating room to provide analgesia and sedation successfully in children undergoing minor surgical procedures such as suturing lacerations and closed reduction of fractures.[46] Although easily administered by untrained personnel, caution should be urged in the use of nitrous oxide without proper instruction and supervision. Inhalation of high concentrations of nitrous oxide may lead to an altered state of consciousness and therefore should not be used in situations in which this might be dangerous, e.g., patients with a full stomach or patients receiving sedative medications in whom the risk of respiratory depression is increased.

Treatment of the discomfort of lumbar puncture and bone marrow aspiration should take into account the fact that these children often have several invasive procedures in store for them. Care must be taken that these procedures cause as little stress as possible. EMLA has been shown to substantially reduce the pain of lumbar puncture in children.[53] Analgesia and anxiolysis for bone marrow aspiration in children may be provided by a combination of oral flunitrazepam, 0.1 mg/kg, up to 2 mg given 90 minutes before the procedure, followed by increments of intravenous fentanyl, 1 μg/kg up to 5 μg/kg.[78] Although not reported for this use, nitrous oxide may also be efficacious in children undergoing lumbar puncture and bone marrow aspiration.

Techniques of providing analgesia and sedation for interventional cardiologic procedures were recently reviewed.[73] Ketamine remains the most popular anesthetic agent for this purpose and the reasons given were the lack of significant hemodynamic changes during cardiac catheterization and the relative maintenance of functional residual capacity during its use. A high incidence of respiratory complications was reported and may have been related to the concomitant use of sedative drugs. Other techniques of providing analgesia for these cardiologic procedures include the use of CM3 (1 mL contains meperidine, 25 mg; chlorpromazine, 6.25 mg; and promethazine, 6.25 mg), inhaled anesthesia, and opioids. The authors stressed the importance of individualizing the sedative/anesthetic technique to meet the requirements of the child's cardiac anomaly and clinical condition and the cardiologist. There does not appear to be one ideal technique.

Limb fractures occur commonly in children and are frequently managed by closed reduction in the emergency department. Analgesia for this procedure, usually an intramuscularly administered "cocktail" consisting of mixtures of opioids and sedatives, is often inadequate. Performance of a regional block with local anesthetic, resulting in analgesia and relaxation of the affected limb before manipulation, provides ideal circumstances for both the patient and the treating physician. Femoral nerve block using 2 mg/kg of 0.5% bupivacaine without epinephrine provided analgesia for 2 hours to 13 of 14 children undergoing radiologic examination and application of traction for femoral shaft fractures.[100] The only complication was one femoral arterial puncture that had no sequelae. The authors also use brachial plexus block to allow painless reduction of upper limb fractures in children in the emergency department.

Perioperative Acute Pain

Preinduction

Drugs given in the preinduction period to alleviate anxiety, such as nasally administered sufentanil and oral transmucosal fentanyl citrate, may also be useful in the management of postoperative pain. Significantly fewer children who received 1.5 to 4.5 μg/kg nasally administered sufentanil preoperatively required analgesics in the postanesthetic recovery room when compared with children who had received placebo.[57] Oral transmucosal fentanyl citrate, used as a premedication, also has been shown to result in decreased narcotic requirement postoperatively.[91] Painless venipuncture before the induction of anesthesia may be achieved by EMLA or nitrous oxide as previously discussed.

Opioid Analgesics

In children, opioids have been administered orally,[92] intravenously by bolus and infusion,[9] nasally,[57] subcutaneously,[88] intramuscularly, rectally,[129] and epidurally.[1] There are differences in pharmacokinetics and pharmacodynamics between adults and children, but these are mainly limited to the first month of life and are discussed in the following sections.

Morphine

Following a study in newborns, which demonstrated increased respiratory sensitivity,[126] physicians have been reluctant to prescribe morphine to infants. Morphine kinetics were studied in children aged 0 to 15 years and no major age differences were found.[22] Other authors have reported that infants 1 to 4 days of age showed longer elimination half-lives (6.8 versus 3.9 hours) and clearance values (6.3 versus 23.8 mL/min/kg),[72] with maturation occurring by 1 month of age. The difference in neonatal pharmacokinetics was confirmed by others who administered an infusion of 20 μg/kg/h for 24 hours in 12 newborns and measured a threefold increase in serum level compared with older infants.[65] A bolus administration of 50 to 100 μg/kg of morphine followed by infusion of 32 and 40 μg/kg/h resulted in even higher serum levels and was complicated by seizures in two of four patients. There was marked variability in the kinetic profile, with one 2-day-old premature infant having a morphine elimination half-life of 28 hours. The authors recommended an infusion rate of 15 μg/kg/h with no loading bolus for neonatal postoperative analgesia. It is also postulated that the neonatal blood–brain barrier is more permeable to morphine, allowing much higher CSF levels to occur.[69] These findings may explain the observation that neonates are more susceptible to respiratory depression following morphine administration. At some time in early infancy, the blood–brain barrier becomes relatively impermeable to water-soluble drugs like morphine.

Fentanyl

Fentanyl use in children increased following the report by Robinson and Gregory,[98] who used it for anesthesia in preterm infants undergoing ligation of patent ductus arteriosus. Singleton and his group found that neonates had an age-related increase in the clearance of fentanyl, most of which had occurred by 2 weeks of age.[112] Infants 3 to 10 months of age had lower plasma concentrations following fentanyl administration compared with children or adults. Neonates following abdominal surgery tended to have prolonged fentanyl clearance, and it was postulated that decreased liver blood flow, possibly combined with patency of the ductus venosus, was responsible.[42] The age-related increase in clearance of fentanyl also may be due to a change in activity of the enzyme responsible for its metabolism. Infants aged 3 months or older were no more sensitive to ventilatory depression than children or adults, although one infant, under 3 months of age, had respiratory depression requiring naloxone.[59]

Yaster[135] investigated the dose response of fentanyl, using hemodynamic response to surgical stimulus as the measure of fentanyl requirements. He found that a bolus of fentanyl, 10 to 12.5 μg/kg, produced insignificant hemodynamic changes and provided reliable anesthesia for 75 minutes, although hemodynamic stability may not be a reliable sign of adequate anesthesia in the premature infant.[2]

Sufentanil

A pharmacokinetic study of sufentanil[45] found that neonates had a clearance rate of 6.7 ± 6.1 mL/kg/min compared with 18.1 ± 2.7, 16.9 ± 3.2, and 13.1 ± 3.6 mL/kg/min observed in infants, children, and adolescents, respectively. The elimination half-lives were 783, 214, 140, and 209 minutes, respectively. The plasma concentration of sufentanil at which further anesthetic supplementation was required for neonates was 2.51 ng/mL and 1.58, 1.53, and 1.56 ng/mL, respectively, for the other groups. In a subsequent study, the authors reported on maturation changes in sufentanil pharmacokinetics,[44] with an increase in clearance, a decrease in half-life, and a slight increase in volume of distribution found in three of the neonates who required a second procedure at 3 to 4 weeks of age.

Methadone

Following its use in adults[43] methadone pharmacokinetics were investigated in children and adolescents.[8] The distribution half-life was 19.2 ± 13.6 hours. Patients given 0.2 mg/kg of methadone intraoperatively had analgesia for 12 to 36 hours postoperatively when compared with morphine, it was found that methadone produced equivalent analgesia, with fewer supplementary injections required in the postoperative period.[6]

Codeine

Approximately 60% of codeine is bioavailable following oral ingestion. The analgesic effect occurs in 20 minutes, reaching a maximum at

60 to 120 minutes. The plasma half-life is 2 to 4 hours. Approximately 10% is demethylated to form morphine, which is responsible for its analgesic effect.[60] It is widely used in combination with acetaminophen, but is a weak analgesic.

Patient-Controlled Analgesia

Sechzer[108, 109] first thought of using patient-controlled analgesia (PCA) while attending a conference on drug addiction at Baylor University College of Medicine in 1965, and his experience with PCA was first published in 1967. Successful use of PCA in children was described in abstract form in 1987[17] and further reports soon followed.[33, 41, 87, 121] Rodgers et al[99] studied 15 children aged 10 to 18 years treated with PCA following major surgery. Analgesic requirements were compared retrospectively with a group who had undergone similar surgery. PCA patients received approximately 0.724 mg/kg/d of morphine on the first day of surgery compared with 0.32 mg/kg/d using conventional intramuscular on-demand injections. On subsequent days PCA patients received less morphine.

A randomized prospective trial comparing intramuscular morphine, PCA morphine, and PCA morphine plus a low-dose continuous infusion studied a total of 82 patients aged between 7 and 19 years undergoing orthopedic procedures.[9] Dosages used were (1) IM group, morphine sulfate, 0.1 to 0.18 mg/kg/h as needed; (2) PCA only, bolus dose of 0.025 mg/kg, lockout time of 10 minutes, and 4-hour limit of 0.24 mg/kg; and (3) PCA plus infusion, bolus of 0.018 mg/kg, continuous infusion of 0.015 mg/kg/h, lockout time of 10 minutes, and 4-hour limit of 0.24 mg/kg. The continuous rate represented 30% to 50% of the average hourly requirements of children receiving continuous infusions for postoperative pain or cancer pain in previous studies.[13, 71, 89] There was no statistical difference in the mean morphine requirements, which averaged 0.026 mg/kg/h. Female patients received more morphine than male patients. There was no difference in the incidence of nausea, time to return of gastrointestinal function, or urinary retention, and there were no respiratory complications. Patients who received PCA plus infusion were significantly less sedated than the intramuscular morphine group and had lower pain scores than either intramuscular or PCA morphine alone. Three patients failed to give a self-administered dose in spite of having pain and adequate preoperative teaching. Although nurse and patient pain scores were significantly correlated, nurses consistently underrated the degree of pain. This phenomenon has been reported in other studies.[127]

The enhanced safety of PCA lies in the fact that the patient is the only person allowed to operate the machine.[40] However, this leaves patients with physical, mental, or developmental handicaps without the potential benefits of PCA analgesia. A recent abstract[14] described successful use of parent-assisted PCA in 22 patients aged 5 to 10 years, although one parent reported the PCA experience as exceptionally stressful. Nurse-administered boluses in patients receiving PCA therapy has also been advocated.[34]

There have been no reports of deaths due to the use of a PCA device in the pediatric age group, although this has occurred in adults.[68] Berde et al[9] noted that only 2 of 550 patients receiving PCA in their unit had significant hypoventilation. We had one patient with significant hypoventilation due to overdose secondary to a combination of improper dilution of the PCA drug and nurse-administered boluses for agitation, which in retrospect was possibly due to hypoxemia. It is recommended that commercially prepared PCA medication be used or that it be prepared by a pharmacist in hospital. If nurse- or parent-assisted boluses are allowed, it is essential that proper education take place, and in these circumstances it would seem prudent to monitor these patients with a pulse oximeter.

Nonopioid Analgesics

Acetaminophen

The relationship between the analgesic effect of acetaminophen and serum concentration in children is unknown, but concentrations between 66.2 and 132.4 μmol/L have an antipyretic effect.[130] When 20 mg/kg was given as an aqueous solution rectally, the mean serum level at 30 minutes was 35.1 ± 15.9 μmol/L.[39] This dose did not provide adequate analgesia for adenotonsillectomy patients in the recovery room. The maximum concentration of 72.2 ± 11.3 μmol/L was not reached until after 120 minutes. When 20 mg/kg is given orally, maximal concentrations of 130.4 ± 30.5 μmol/L do occur by 30 minutes, but it is not known whether this provides analgesia.

Nonsteroidal Anti-inflammatory Drugs

Indomethacin

An intravenous bolus of indomethacin, 0.35 mg/kg intravenously, followed by an infusion of 0.07 mg/kg/h for 24 hours given to children undergoing orthopedic procedures meant that they required significantly less morphine in the postoperative period. No complications attributable to indomethacin occurred.[77]

Ketorolac

Ketorolac is a new nonsteroidal anti-inflammatory drug that exhibits potent analgesia, but only moderate anti-inflammatory activity. Advantages include lack of respiratory depression, gastrointestinal atonia, addiction, or psychomotor effects. Potential problems include gastric and duodenal ulceration, bronchospasm, and impaired renal and platelet function.[95] Further investigation is needed in the pediatric population.

Regional Blockade

Regional blocks are easy to perform in children. They may be used for preoperative, operative, or postoperative analgesia. Always calculate and never exceed the maximum safe dose per kilogram of local anesthetic. For detailed information about technique, the reader is referred to articles by Dalens[25] and Sethna and Berde.[110]

Local Anesthetic Drugs

There are age-related differences in the pharmacokinetics of hydrophilic drugs like local anesthetics.[25] In infants the volume of distribution and the elimination half-life are increased. The levels of albumin and α_1-acid glycoprotein are lower, resulting in an elevated free fraction of drug. Neonates may be at increased risk of toxicity as a result of an elevated free fraction of local anesthetic, but this may be offset by their larger volume of distribution.

Delayed metabolism of amide drugs can occur due to decreased liver enzyme activity, and ester local anesthetic metabolism can be prolonged by decreased plasma cholinesterase.[139] Small infants may fail to metabolize breakdown products of prilocaine, resulting in methemoglobinemia, and this has been described with the use of EMLA.[61]

Cervical Plexus Block

Blockade of the cervical plexus results in anesthesia of the head and neck (except for the area supplied by the cranial nerves), which extends down to the upper chest. We have successfully used a modified interscalene approach[132] to provide anesthesia and analgesia for three children undergoing scalene node biopsy for diagnosis of anterior mediastinal tumor (unpublished).

Interpleural Local Anesthesia

Reiescad and Stromskag[96] first reported the use of interpleural regional anesthesia. A 24-hour continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine via an interpleural catheter at 0.5 mL/kg/h to children following thoracotomy provided excellent analgesia.[85] Five patients had asymptomatic blood bupivacaine levels over 4 μg/mL, with one patient having a concentration over 7 μg/mL. These levels are beyond the normal accepted safe adult range of 2 to 4 μg/mL. The lack of toxicity may be explained by a gradual rate of increase in plasma concentration.[105] Adult studies have shown decreased systemic absorption when bupivacaine with epinephrine 1:200,000 is used.[20, 63] Mechanical ventilation may decrease hepatic blood flow, resulting in delayed elimination of interpleural local anesthetics.[19]

Brachial Plexus Block

Supraclavicular brachial plexus block in children was first reported by Farr in 1920.[37] A parascalene technique for use in children was recently reported.[24] Using a nerve stimulator for localization of the plexus, analgesia was achieved in 97% of patients compared with 88% using a classical approach. An interscalene technique[131] or axillary approach can also be used.[18] If a tourniquet is required, the supraclavicular route may be preferable. Individual nerves can also be blocked at the antecubital fossa or wrist.

Intravenous Regional Block

Upper limb fractures in patients aged 3 to 15 years have been reduced under intravenous regional anesthesia.[120] A dose of 3 mg/kg of 0.5% lidocaine was used. Analgesia was described as good in 72% and fair in 18%. One child complained of transient dizziness and circumoral paresthesia following failure of the tourniquet. A pediatric fatality has been reported following a Bier block.[56]

Intercostal Nerve Block

Children aged 3 months to 16 years were given intercostal blocks with bupivacaine, 2 to 4 mg/kg, for postoperative analgesia.[101] Peak serum levels occurred between 5 and 10 minutes following injection and the highest level recorded was 3.2 μg/mL in a patient given 4 mg/kg. The authors recommended 4 mg/kg as the upper dose limit of bupivacaine for intercostal block. No complications were reported. A study in adults found that a single-dose interpleural block provided a shorter duration of postoperative analgesia than following intercostal block. In addition, the plasma concentration of local anesthetic was significantly higher after the interpleural block.[123] There have been no comparisons of interpleural with intercostal blocks in children. Intercostal blocks may be used for analgesia for rib fractures, cholecystectomies, and following thoracotomy.

Ilioinguinal/Iliohypogastric Block

Postoperative analgesia for inguinal herniorrhaphy may be provided by ilioinguinal/iliohypogastric block.[70] A comparison between this block and installation of bupivacaine into the wound showed no difference in pain scores or analgesic requirements in the recovery room. Plasma bupivacaine concentrations during caudal block and ilioinguinal/iliohypogastric nerve block were compared, and it was found that the uptake of bupivacaine was more rapid following ilioinguinal block than during caudal analgesia. Both groups had serum bupivacaine concentrations of less than 1 μg/mL.[117]

Lumbar Plexus Block

Two techniques of lumbar plexus block were evaluated in 50 children undergoing surgery in the hip region.[27] Predictable anesthesia occurred when twitches were elicited during performances of the block. The technique described by Winnie et al[132] was preferred. An alternative to this technique is to administer a caudal block.

Femoral Nerve Block

This has been reported for use in patients with a fractured shaft of the femur.[47, 55, 100] The technique provides rapid, effective, prolonged analgesia, allowing reduction and stabilization to occur in comfort and is suitable for instituting in the emergency department using the usual precautions.

Sciatic Nerve Block

McNicol[86] reported 95% success in blocking the sciatic nerve with an anterior approach, and reliable postoperative analgesia was provided for operations in the foot and ankle. Three different approaches to the sciatic nerve were compared in 180 pediatric patients.[23] The authors concluded that the posterior and lateral approaches are the most suitable technique for blocking the sciatic nerve proximally. Anesthesia was similar and included the sciatic nerve and posterior femoral cutaneous nerve distribution. The lateral approach is indicated when patients cannot lie on their side.

Penile Block

Penile block is an alternative to caudal analgesia following circumcision.[114] It is easy to perform and successful in 96% of patients. Potential complications include hematoma and rapid absorption of anesthetic agent. The efficacy of intravenous morphine, penile block, and the application of local anesthetic for analgesia in circumcised patients was compared.[119] Topical analgesia was found to be effective in 95% and had a similar duration to morphine and nerve block and could be repeated on an as-needed basis. A comparison between caudal block and penile block found the degree of anesthesia similar, but the caudal block had a higher incidence of motor blockade.[136] Gangrene following a dorsal nerve block in the penis has been reported.[103]

Epidural

Effective analgesia for a variety of procedures may be provided by epidurally administered local anesthetics and opioids. Medication given via the lumbar approach to the epidural space has been shown to provide analgesia for upper and lower abdominal procedures, as well as for those on the lower limbs.[28] A catheter can be threaded into the epidural space at this level to allow continuous infusion of local anesthetics and opioids.[32] The advantages of this technique of continuous delivery of analgesic medication are the lower likelihood of periods of inadequate analgesia and decreased risk of toxicity due to sudden high levels of medication following bolus injection. The sacral approach (caudal) is very commonly used in children and has been shown to be safe, with few side effects.[15, 26] A caudal block is generally used in younger children, i.e., less than 7 years of age, and medication is usually given as a single shot, not via a catheter. Using this approach, effective analgesia can be provided for lower abdominal, urologic, and lower limb pain.[12, 54, 79, 116] The thoracic and cervical approaches have more possible associated risks and should be limited to special circumstances.

The anatomy of the neuraxis in young children differs from that in adults.[29] In children less than 1 year of age the lower end of the spinal cord occurs near the L3–4 interspace, and the dural sac at S3–4. With growth, the cord reaches the adult level of L1–2 and the dural sac, S1–2. Up to approximately 8 years of age the contents of the epidural space are more loosely packed, which may allow greater spread of local anesthetic and the ability to thread a catheter epidurally from the caudal space to the thoracic area. The skin-to-epidural space distance is shorter and the volume of CSF is greater per kilogram of body weight in children. Smaller needles and epidural catheters are available for performing an epidural block in pediatric patients.

Performance of an epidural block for postoperative analgesia usually takes place while the child is asleep for the surgical procedure. Blocks placed immediately following induction of anesthesia offer the advantage of decreasing intraoperative anesthetic requirements and in the case of caudal block, this does not shorten the duration of postoperative analgesia, which appears to be at least 4 to 6 hours.[97] The use of epinephrine as a test dose to rule out intravascular injection of local anesthetic may not be reliable in children anesthetized with halothane.[31] The administration of intravenous atropine before the epidural test dose improves the reliability, but not to 100%. Therefore, it is important to give the local anesthetic slowly and watch for signs of intravascular injection. The reader is referred to some excellent descriptions of the technique of performing an epidural block in children.[29, 110]

There are many formulae to calculate the caudal local anesthetic dose necessary to achieve specific dermatomal levels,[4, 104, 118] but it appears that a volume of 0.75 to 1.0 mL/kg[26] and a bupivacaine concentration of 0.125% to 0.25%[50, 134] provides the most reliable analgesia for pain up to the T10 dermatome, with the least amount of toxicity and side effects. Morphine has also been given via the caudal route to provide analgesia following abdominal, urologic, lower extremity, and cardiac surgery.[62, 66, 102, 122] In doses ranging from 0.05 to 0.1 mg/kg it provides effective analgesia, with significantly decreased analgesic requirements for up to 24 hours postoperatively, but it may be associated with side effects, such as urinary retention, pruritus, nausea and vomiting, and early and late respiratory depression.[67] Patients who have received morphine epidurally, via either the caudal or epidural routes, should be monitored for respiratory depression for at least 24 hours following the most recent dose.

Following catheter placement in the lumbar epidural space, local anesthetic is probably most effective given as a continuous infusion. A bolus of 0.5 mL/kg of bupivacaine 0.25% followed by an infusion of 0.08 mL/kg/h provided analgesia to a dermatomal level between T10 and L1 in 21 children who underwent orthopedic and urologic procedures.[32] Morphine, 0.05 mg/kg, gives good prolonged analgesia when injected through a lumbar epidural catheter, but has been shown in children to decrease the ventilatory response to CO_2 for up to 22 hours.[1] Continuous epidural infusions of bupivacaine 0.1% to 0.125% and fentanyl, 2 μg/mL, may provide analgesia with the advantage of decreased risk of respiratory depression and local anesthetic toxicity due to the lower concentrations of each drug used.[7]

Acute Pain in Sickle Cell Disease

A vaso-occlusive crisis in sickle cell disease produces severe acute pain in a patient already burdened with a chronic disease. In the management of this pain, hospitalization is avoided, if possible, with emphasis on behavior therapy, with family support, hydration, and oral analgesics, such as codeine. If hospital admission becomes necessary, intravenous opioids are often administered.[21] PCA is well suited for the management of older patients and its use has been reported for pain of a vaso-occlusive crisis.[106]

CONCLUSION

Children do experience pain and techniques have been developed to provide analgesia for all age groups. Many of the age-related differences in response to treatment have been documented. Side effects of treatment do occur and the risk-to-benefit ratio should be considered. Future research will define safe monitoring practices for specific techniques.

ACKNOWLEDGMENT

The authors would like to thank Joanne Zabihaylo and Roula Cacolyris for their excellent technical assistance and Joan Bunke for her support.

References

1. Attia J, Ecoffey C, Sandouk P, et al: Epidural morphine in children: Pharmacokinetics and CO_2 sensitivity. Anesthesiology 65:590–594, 1986
2. Anand KJS, Sippell WG, Aynsley-Green A: Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: Effects on the stress response. Lancet 1:243–247, 1987
3. Anand KJS, Hickey PR: Pain and its effects in the human neonate and fetus. N Engl J Med 317:1321–1328, 1987
4. Armitage EN: Caudal block in children. Anaesthesia 34:396, 1979
5. Bennet RL, Batenhorst RL, Bivins BA, et al: Patient-controlled analgesia: A new concept of postoperative pain relief. Ann Surg 195:700–705, 1981
6. Berde CB, Holzman RS, Sethna NF, et al: A comparison of methadone and morphine for postoperative analgesia in children and adolescents. Anesthesiology 67:A519, 1987
7. Berde CB, Sethna NF, De Jesus JM, et al: Continuous epidural bupivacaine-fentanyl infusions in children undergoing urologic surgery. Anesth Analg 70:S22, 1990
8. Berde CB, Sethna NF, Holzman RS, et al: Pharmacokinetics of methadone in children and adolescents in the perioperative period. Anesthesiology 67:A519, 1987
9. Berde CB, Lehn BN, Yee JD, et al: Patient-controlled analgesia in children and adolescents: A randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. J Pediatr 118:3:460–466, 1991
10. Beyer J, Aradine C: Content validity of an instrument to measure young children's perceptions of the intensity of their pain. J Pediatr Nur 1:386–395, 1986
11. Beyer J, DeGood D, Ashley L, et al: Patterns of postoperative analgesia use with adults and children following cardiac surgery. Pain 17:71–81, 1983
12. Blaise G, Roy WL: Postoperative pain relief after hypospadius repair in pediatric patients: Regional analgesia versus systemic analgesics. Anesthesiology 65:84–86, 1986
13. Bray RJ: Postoperative analgesia provided by morphine infusion in children. Anaesthesia 38:1075–1078, 1983
14. Broadman LN, Rice LJ, Vaughan M, et al: Parent-assisted PCA for postoperative pain control in young children. Anesth Analg 70:S34, 1990
15. Broadman LM, Hannallah RS, Norden JM, et al: "Kiddie caudals" experience with 1154 consecutive patients without complications. Anesth Analg 66:S18, 1987
16. Brogden RN: Nonsteroidal anti-inflammatory analgesics other than salicilates. Drugs 4:27–45, 1986
17. Brown RE, Broadman LM: Patient-controlled analgesia (PCA) for postoperative pain control in adolescents. Anesth Analg 66:S22, 1987
18. Campbell RJ, Ilett KF, Dusci L: Plasma bupivacaine concentrations after axillary block in children. Anaesth Intensive Care 14:343–346, 1986
19. Carli P, Duranteau J, Mazoit X, et al: Pharmacokinetics of interpleural lidocaine administration in trauma patients. Anesth Analg 70:448–453, 1990
20. Chan TGK, Kan AF, Gregory MA, et al: Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. Br J Anaesth 64:662–666, 1990
21. Cole TB, Sprinkle RH, Smith SJ, et al: Intravenous narcotic therapy for children with severe sickle cell crisis. Am J Dis Child 140:1255–1259, 1986
22. Dahlstrom B, Bolme P, Feychting H, et al: Morphine kinetics in children. Clin Pharmacol Ther 26:3:354–365, 1979
23. Dalens B, Tanguy A, Vaneuville G: Sciatic nerve blocks in children: Comparison of the posterior, anterior and lateral approaches in 180 pediatric patients. Anesth Analg 70:131–137, 1990
24. Dalens B, Vanneuville G, Tanguy A: A new parascalene approach to the brachial plexus in children: Comparison with the supraclavicular approach. Anesth Analg 66:1264–1271, 1987
25. Dalens B: Pediatric Regional Anesthesia. Boca Raton, Florida, CRC Press, 1990
26. Dalens B, Hasnaoui A: Caudal anesthesia in pediatric surgery: Success rate and adverse effects in 750 consecutive patients. Anesth Analg 68:83–89, 1989

27. Dalens B, Tanguy A, Vanneuville G: Lumbar plexus block in children: A comparison of two procedures in 50 patients. Anesth Analg 67:750–758, 1988
28. Dalens B, Tanguy A, Haberer J-P: Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth Analg 65:1069–1073, 1986
29. Dalens B: Blocks along the neuraxis: *In* Dalens B (ed): Pediatric Regional Anesthesia. Boca Raton, Florida, CRC Press, 1990, p 229
30. Dalens B: Regional anesthesia in children. Anesth Analg 68:654–672, 1989
31. Desparmet J, Mateo J, Ecoffey C, et al: Efficacy of an epidural test dose in children anesthetized with halothane. Anesthesiology 72:249–251, 1990
32. Desparmet J, Meistelman C, Barre J, et al: Continuous epidural infusion of bupivacaine for postoperative pain relief in children. Anesthesiology 67:108–110, 1987
33. Dodd E, Wang JM, Rauck RL: Patient-controlled analgesia for post-surgical pediatric patients ages 6–16 years. Anesthesiology 69:A372, 1988
34. Doyle L: Patient-controlled analgesia in the post-anesthesia care unit: One unit's approach. J Post Anesth Nurs 6:2:93–97, 1991
35. Eland JM, Anderson JE: The experience of pain in children. *In* Jacox AK (ed): Pain: A Source Book for Nurses. Boston, Little, Brown, 1977
36. Ewin DM: Emergency room hypnosis for the burned patient. Am J Clin Hypn 29:7–12, 1986
37. Farr RE: Local anesthesia in infancy and childhood. Arch Pediatr 37:381, 1920
38. Fradet C, McGrath PJ, Kay J, et al: A prospective survey of reactions to blood tests by children and adolescents. Pain 40:53–60, 1990
39. Gaudreault P, Guay J, Nicol O, et al: Pharmacokinetics and clinical efficacy of intrarectal solution of acetaminophen. Can J Anaesth 35:149–152, 1988
40. Gaukroger PB: Pediatric analgesia: Which drug? Which dose? Drugs 41:52–59, 1991
41. Gaukroger PB, Tomkins DP, Van der Walt JH: Patient-controlled analgesia in children. Anaesth Intens Care 17:264–268, 1989
42. Gauntlett IS, Fisher DM, Hertzka RE, et al: Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age. Anesthesiology 69:683–687, 1988
43. Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 57:458–467, 1982
44. Greeley WJ, deBruijn NP: Changes in the sufentanil pharmacokinetics within the neonatal period. Anesth Analg 67:86–90, 1988
45. Greeley WJ, deBruijn NP, Davis DP: Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesth Analg 66:1067–1072, 1987
46. Griffin GC, Campbell VD, Jones R: Nitrous oxide-oxygen sedation for minor surgery. JAMA 245:2411–2413, 1981
47. Grossbard GD, Love BRT: Femoral nerve block: A simple and safe method of instant analgesia for femoral shaft fractures in children. Aust NZ J Surg 49:5:592–594, 1979
48. Grossi E, Bourghi C, Cerchiari E, et al: Analog chromatic continuous scale (ACCS): A new method of pain assessment. Clin Exp Rheumatol 1:337–340, 1983
49. Grumau RVE, Craig KD: Pain expressions in neonates: Facial action and cry. Pain 28:395–410, 1987
50. Gunter JB, Dunn CM, Bennie JB, et al: Optimum concentration of bupivacaine for combined caudal-general anesthesia in children. Anesthesiology 75:57–61, 1991
51. Hallen B, Olsson GL, Uppfeldt A: Pain-free venepuncture-effect of timing of application of local anaesthetic cream. Anaesthesia 39:969–972, 1984
52. Hallen B, Uppfeldt A: Does lidocaine-prilocaine cream permit painfree insertion of IV catheters in children? Anesthesiology 57:340–342, 1982
53. Halperin DL, Koren G, Attias D, et al: Topical skin anesthesia for venous, subcutaneous drug reservoir and lumbar punctures in children. Pediatrics 84:281–284, 1989
54. Hassan S: Caudal anesthesia in infants. Anesth Analg 56:686–689, 1977
55. Hood G, Edbrooke DL, Gerrish SP, et al: Postoperative analgesia after triple nerve block for fractured neck of femur. Anaesthesia 46:138–140, 1991
56. Heath M: Death after intravenous regional anaesthesias. Br J Anaesth 285:913–914, 1982
57. Henderson JM, Brodsky DA, Fisher DM, et al: Pre-induction of anesthesia in

pediatric patients with nasally administered sufentanil. Anesthesiology 68:671–675, 1988

58. Henderson JM, Spence DG, Komocar LM, et al: Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. Anesthesiology 72:269–271, 1990
59. Hertzka RE, Gauntlett IS, Fisher DM, et al: Fentanyl-induced ventilatory depression: Effects of age. Anesthesiology 70:213–218, 1989
60. Jaffe JH, Martin WR: Opioid analgesics and antagonists. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacological Basis of Therapeutics. New York, Pergamon Press, 1990, p 485
61. Jakobson B, Nilsson A: Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: A case report. Acta Anaesthesiol Scand 29:453–455, 1985
62. Jensen BH: Caudal block for postoperative pain relief in children after genital operations. A comparison between bupivacaine and morphine. Acta Anaesthesiol Scand 25:373–375, 1981
63. Kambam JR, Hammond J, Parris WCV, et al: Interpleural analgesia for post-thoracotomy pain and blood levels of bupivacaine following interpleural injection. Can J Anaesth 36:106–109, 1989
64. Kimball KL, Drews JE, Walker S, et al: Use of TENS for pain reduction in burn patients receiving travase. J Burn Care Rehab 8:28–31, 1987
65. Koren G, Butt W, Chinyanga H, et al: Postoperative morphine infusion in newborn infants: Assessment of disposition characteristics and safety. Pediatr Pharmacol Ther 107:963–967, 1985
66. Krane EJ, Jacobson LE, Lynn AM, et al: Caudal morphine for postoperative analgesia in children: A comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 66:647–653, 1987
67. Krane EJ: Delayed respiratory depression in a child after caudal epidural morphine. Anesth Analg 67:79–82, 1988
68. Kreitzer JM, Kirschenbaum LP, Eisenkraft JB: Safety of PCA devices. Anesthesiology 70:881, 1989
69. Kupferberg HJ, Way EL: Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. J Pharmacol Exp Ther 141:105–112, 1963
70. Langer JC, Shandling B, Rosenberg M: Intraoperative bupivacaine during outpatient hernia repair. J Pediatr Surg 22:267–270, 1987
71. Lynn AM, Opheim KE, Tyler DC: Morphine infusion after pediatric cardiac surgery. Crit Care Med 12:863–866, 1984
72. Lynn AM, Slattery JT: Morphine pharmacokinetics in early infancy. Anesthesiology 66:136–139, 1987
73. Malviya S, Burrows FA, Johnson AE, et al: Anaesthetic experience with paediatric interventional cardiology. Can J Anaesth 36:320–324, 1989
74. Manner T, Kanto J, Lindberg R, et al: Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): Comparison with placebo cream and no local premedication. Acta Anaesthesiol Scand 31:735–739, 1987
75. Mather L, Mackie J: The incidence of postoperative pain in children. Pain 15:271–282, 1983
76. Maunuksela EL, Korpela R: Double blind evaluation of a lignocaine-prilocaine cream (EMLA) in children. Br J Anaesth 58:1242–1245, 1986
77. Maunuksela EL, Olkkola KT, Korpela R: Does prophylactic intravenous infusion of indomethacin improve the management of postoperative pain in children? Can J Anaesth 35:123–127, 1988
78. Maunuksela EL, Rajantie J, Siimes MA: Flunitrazepam-fentanyl induced sedation and analgesia for bone marrow aspiration and needle biopsy in children. Acta Anaesthesiol Scand 30:409–411, 1986
79. May AE, Wandless J, James RH: Analgesia for circumcision in children. Acta Anaesthesiol Scand 26:331–333, 1982

80. Mazoit JX, Denson DET, Samii K: Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology 68:387–391, 1988
81. McGrath PA, Deveiber LL, Hairn MT: Multidimensional pain assessment in children. *In* Fields HL, Dubner R, Cervero F (eds): Advances in Pain Research and Therapy: Proceedings of the Fourth World Congress on Pain. New York, Raven Press, 1985, pp 387–393
82. McGrath PA: Pain in Children: The Perception, Assessment and Control of Children's Pain. New York, Guilford Press, 1987
83. McGrath PA: An assessment of children's pain: A review of behavioural, physiological and direct scaling techniques. Pain 31:147–176, 1987
84. McGrath PJ, Johnson G, Goodman JT, et al: The CHEOPS: A behavioural scale to measure postoperative pain in children. *In* Fields HL, Dubner R, Cervero F (eds): Advances in Pain Research and Therapy. New York, Raven Press, 1985, p 395
85. McIlvaine WB, Knox RS, Fennessey PV: Continuous infusion of bupivacaine via interpleural catheter for analgesia after thoracotomy in children. Anesthesiology 69:261–264, 1988
86. McNicol LR: Sciatic nerve block for children. Anaesthesia 40:410–414, 1985
87. Means LJ, Allen HM, Lookabill SJ, et al: Recovery room initiation of patient-controlled analgesia in pediatric patients. Anesthesiology 69:A772, 1988
88. Miser AW, Davis DM, Hughes CS, et al: Continuous subcutaneous infusion of morphine in children with cancer. Am J Dis Child 173:383–385, 1983
89. Miser AW, Miser JS, Clark BS: Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. J Paediatr 96:930–932, 1980
90. Morselli PL, Franco-Morselli R, Bosi L: Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. Clin Pharmacokinet 5:485–527, 1980
91. Nelson PS, Streisand JB, Mulder SM, et al: Comparison of oral transmucosal fentanyl citrate and an oral solution of meperedine, diazepam, and atropine for premedication in children. Anesthesiology 70:616–621, 1989
92. O'Hara M, McGrath PJ, D'Astous J, et al: Oral morphine versus injected meperidine (Demerol) for pain relief in children after orthopedic surgery. J Pediatr Orthop 7:78–82, 1987
93. Olness K, Gardner GG: Some guidelines for uses of hypnotherapy in pediatrics. Pediatrics 62:228–233, 1978
94. Paterson DR, Questad KA, Boltwood MD: Hypnotherapy as a treatment for pain in patients with burns: Research and clinical considerations. J Burn Care Rehab 8:263–268, 1987
95. Power I, Noble DW, Douglas E, et al: Comparison of IM ketolorac trometamol and morphine sulfate for pain relief after cholecystectomy. Br J Anaesth 65:448–455, 1990
96. Reiescad F, Stromskag KE: Interpleural catheter in the management of postoperative pain: A preliminary report. Reg Anaesth 11:89–91, 1986
97. Rice LJ, Pudimat MA, Hannallah RS: Timing of caudal block placement in relation to surgery does not affect duration of postoperative analgesia in paediatric ambulatory patients. Can J Anaesth 37:429–431, 1990
98. Robinson S, Gregory GA: Fentanyl-air-oxygen anesthesia for patent ductus arteriosus in preterm infants. Anesth Analg 60:331–334, 1981
99. Rodgers BN, Webb CJ, Stergios D, et al: Patient-controlled analgesia in pediatric surgery. J Pediatr Surg 23:259–263, 1988
100. Ronchi L, Rosenbaum D, Athouel A, et al: Femoral nerve block in children using bupivacaine. Anesthesiology 70:622–624, 1989
101. Rothstein P, Arthur FR, Feldman HS, et al: Bupivacaine for intercostal nerve blocks in children: Blood concentrations and pharmacokinetics. Anesth Analg 65:625–632, 1986
102. Rosen KR, Rosen DA: Caudal epidural morphine for control of pain following open heart surgery in children. Anesthesiology 70:418–421, 1989
103. Sara CA, Lowry CJ: A complication of circumcision and dorsal nerve block of the penis. Anaesth Intens Care 13:79–85, 1984
104. Satoyoshi M, Kamiyama Y: Caudal anaesthesia for upper abdominal surgery in

infants and children: A simple calculation of the volume of local anaesthetic. Acta Anaesthesiol Scand 28:57–60, 1984

105. Scott DB: Evaluation of clinical tolerance of local anesthetic agents. Br J Anaesth 47:328–333, 1975
106. Schechter NL, Berrien FB, Katz SM: The use of patient-controlled analgesia in adolescents with sickle cell pain crisis: A preliminary report. J Pain Sympt Manag 3:109–113, 1988
107. Schechter NL, Allen DA, Hanson K: Status of pediatric pain control: A comparison of hospital analgesic usage in children and adults. Pediatrics 77:11–15, 1986
108. Sechzer PH: Patient-controlled analgesia (PCA): A retrospective. Anesthesiology 72:735–736, 1990
109. Sechzer PH: Objective measures of pain and pain relief following cardiovascular surgery. Rev Argent Angiology 1:9–12, 1967
110. Sethna NF, Berde CB: Pediatric regional anesthesia. *In* Gregory GA (ed): Pediatric Anesthesia, ed 2. New York, Churchill Livingstone, 1989, p 647
111. Sfez M, Mapihan YL, Mazoit X, et al: Local anesthetic concentrations after penile nerve block in children. Anesth Analg 71:423–426, 1990
112. Singleton MA, Rosen JI, Fisher DM: Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth 34:152–155, 1987
113. Sloan JP, Muwanga CL, Waters EA, et al: Multiple rib fractures: Transcutaneous nerve stimulation versus conventional analgesia. J Trauma 26:1120–1122, 1986
114. Soliman MG, Tremblay NA: Nerve block of the penis for postoperative pain relief in children. Can J Anaesth 57:495–498, 1978
115. Soliman IE, Broadman LM, Hannallah RS, et al: Comparison of the analgesic effects of EMLA (eutectic mixture of local anesthetics) to intradermal lidocaine infiltration prior to venous cannulation in unpremedicated children. Anesthesiology 68:804–806, 1988
116. Soliman MG, Ansara S, Laberge R: Caudal anaesthesia in paediatric patients. Can J Anaesth 25:226–230, 1978
117. Stowe PJ, Scott A, Phillips A, et al: Plasma bupivacaine concentrations during caudal analgesia and ilioinguinal/iliohypogastric nerve block in children aged 3 to 7 years. Anaesthesia 43:650–653, 1988
118. Takasaki M, Dohi S, Kawabata Y, et al: Dosage of lidocaine for caudal anesthesia in infants and children. Anesthesiology 47:527–529, 1977
119. Tree-Trakarn T, Pirayavaraporn S: Postoperative pain relief for circumcision in children: Comparison among morphine, nerve block, and topical analgesia. Anesthesiology 62:519–522, 1985
120. Turner PL, Batten JB, Hjorth D, et al: Intravenous regional anesthesia for the treatment of upper limb injuries in childhood. Aust NZ J Surg 56:153–155, 1986
121. Tyler TC: Patient-controlled analgesia in adolescence. Pain Suppl 4:S233, 1987
122. Valley RD, Bailey AG: Caudal morphine for postoperative analgesia in infants and children: A report of 138 cases. Anesth Analg 72:120–124, 1991
123. van Kleef JW, Burm AGL, Vletter AA: Single-dose interpleural vs intercostal blockade: Nerve block characteristics and plasma concentration profiles after administration of 0.5% bupivacaine with epinephrine. Anesth Analg 70:484–488, 1990
124. Wakeman RJ, Kaplan JZ: An experimental study of hypnosis in painful burns. Am J Clin Hypn 21:3–11, 1978
125. Wasz-Hockert O, Lind J, Vuorenkoski V, et al: The infant cry: A spectro-graphic and auditory analysis. Clin Dev Med 29:9–42, 1968
126. Way WL, Costley EC, Way EL: Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Ther 6:454–461, 1965
127. Webb CJ, Stergios DA, Rodgers BM: Patient-controlled analgesia as postoperative pain treatment for children. J Pediatr Nurs 4:3:162–171, 1989
128. Weissman C: The metabolic response to stress: An overview and update. Anesthesiology 73:308–327, 1990
129. Westerling D: Rectally administered morphine: Plasma concentration in children premedicated with morphine in hydrogel and in solution. Acta Anaesthesiol Scand 29:653–656, 1985
130. Windofer A, Vogel C: Investigations concerning serum concentration and temperature following oral application of a new paracetamol preparation. Klin Paediatr 188:430–434, 1976

131. Winnie AP: Interscalene brachial plexus block. Anesth Analg 49:455–466, 1970
132. Winnie AP, Ramamurthy S, Durrani Z, et al: Plexus blocks for lower extremity surgery. Anesthesiol Rev 1:11–16, 1974
133. Winnie AP, Ramamurthy S, Durrani Z, et al: Interscalene cervical plexus block: A single-injection technique. Anesth Analg 54:370, 1975
134. Wolf AR, Valley RD, Fear DW, et al: Bupivacaine for caudal analgesia in infants and children: The optimal effective concentration. Anesthesiology 69:102–106, 1988
135. Yaster N: The dose response of fentanyl in neonatal anesthesia. Anesthesiology 66:433–435, 1987
136. Yeoman PN, Cooke R, Hain WR: Penile block for circumcision? A comparison with caudal blockade. Anesthesia 38:862–866, 1983
137. Zeltzer L, Dash J, Holland JP: Hypnotically induced pain control in sickle cell anemia. Pediatrics 64:533–536, 1979
138. Zeltzer L, LeBaron S: Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. J Pediatr 101:1032–1035, 1982
139. Zsigmond EK, Downs JR: Plasma cholinesterase activity in newborns and infants. Can Anaesth Soc J 18:278, 1971

Address reprint requests to

Desmond G. Spence, MD
Department of Anaesthesia
Montreal Children's Hospital
2300 Tupper Street
Montreal, Quebec
Canada HPH 1P3

CURRENT CONCEPTS IN ACUTE PAIN CONTROL 0889-8537/92 $0.00 + .20

OBSTETRIC PAIN MANAGEMENT

Graham H. McMorland, MB, ChB, DA, FRCPC

Relief of the pain of labor has been controversial ever since the Scottish obstetrician, James Young Simpson, first administered ether for internal podalic version and delivery of a dead fetus, in a woman with an inadequate pelvis. Criticism of his attempts to relieve labor pain came from clergymen and some physicians. Modern obstetric anesthetists still have to contend with opposition, but now it comes mainly from community activists.

In recent years there has been a movement to encourage pregnant women to prepare for a drug-free labor and birth. The concept is commendable, and it is certainly true that many parturients, after uncomplicated pregnancies, are able to experience well-controlled, uneventful labor without resort to pharmacologic analgesia. However, drug-free labor cannot be equated with painless labor. Melzack et al[37] have shown that, even after/careful prenatal preparation for controlled childbirth, most women do experience pain during labor. Their preparation, then, is aimed at coping with, rather than preventing, pain.

Many parturients experience long, exhausting, sometimes difficult labor. Maternal exhaustion may be accompanied by anxiety and hyperventilation, with progressive increase in endogenous catecholamine secretion. Maternal catecholamine levels have been demonstrated to increase, even during uncomplicated labor, to levels that are significantly higher than those seen in late pregnancy.[30] Those parturients who are most anxious and exhausted will have higher levels of plasma catecholamines, with consequently decreased uterine activity and longer labors.[29] These women manifest an increased incidence of abdormal fetal heart rate patterns, and their babies tend to have lower Apgar scores.[28]

From the Division of Obstetric Anaesthesia and Pharmaceutical Sciences, The University of British Columbia; and Department of Anaesthesia, The Salvation Army Grace Hospital, Vancouver, British Columbia, Canada

These observations have been confirmed by animal studies.[41, 42, 57] The increased endogenous catecholamine secretion that follows maternal stress results in diminished uterine blood flow and may even lead to acute fetal asphyxia. In human parturients, Shnider et al[55] demonstrated a 56% reduction in maternal plasma epinephrine following administration of lumbar epidural analgesia during labor. Hagerdal et al[19] showed that oxygen consumption and minute ventilation increased during labor by 63% and 74%, respectively. These increases were abolished, or decreased, by lumbar epidural analgesia. These studies suggest that when nonpharmacologic techniques of pain management prove to be ineffective or inadequate during labor, well-managed chemical analgesia will reduce stress and be beneficial for mother, fetus, and neonate.

LABOR PAIN PATHWAYS

The pain of the first stage of labor is mainly due to dilatation of the cervix, with stretching of the fibers of the cervix and lower uterine segment. There is also evidence that contractions of the body of the uterus contribute to labor pain.[6] The afferent fibers accompany the sympathetic nerves and enter the T10 to L1 spinal segments. Pain sensation is referred to the dermatomes supplied by these spinal cord segments.

During the second stage of labor, stretching of the pelvis and perineum causes pain, in addition to the continued pain of the uterine contractions. These pelvic and perineal pain impulses travel via the pudendal nerves, to enter the neuraxis at the S2, S3, and S4 segments (Fig. 1).

ANALGESIA FOR LABOR AND VAGINAL BIRTH

Psychoprophylaxis

Psychoanalgesia relies on personal motivation, as well as prenatal education regarding the childbirth process. The reduction of the fear and anxiety associated with the unknown enables the parturient to cope better with labor pain. This technique of analgesia is not as predictable in its efficacy as other methods of pain relief.

While Melzack et al[37] have shown that prenatal preparation for labor does not abolish pain and many women will request some form of analgesia, it does make the experience more satisfying for women and, for this reason, is well worth the effort.

Transcutaneous Electrical Nerve Stimulation

The mechanism of action of transcutaneous electrical nerve stimulation is not known. The "gate" control theory of pain, propounded by

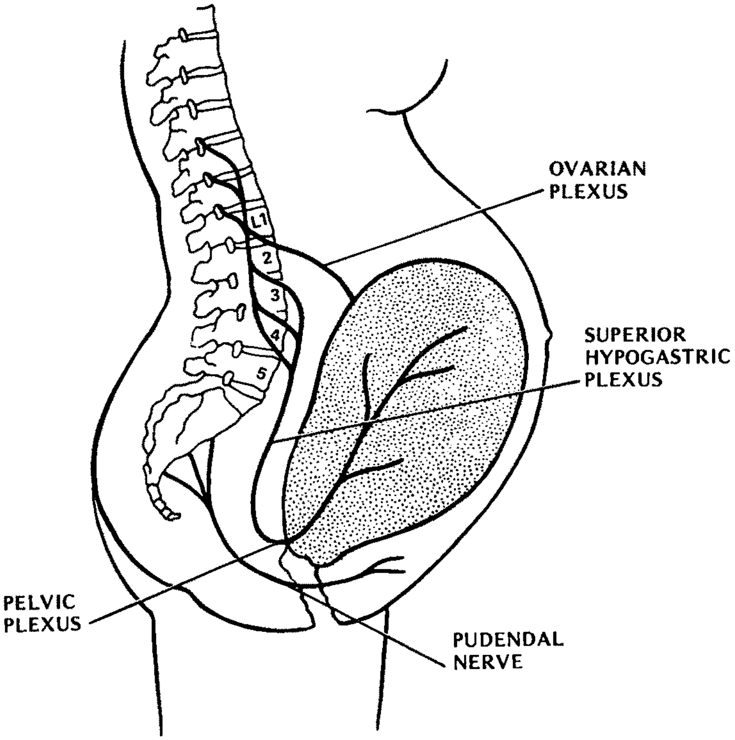


Figure 1. Labor-pain pathways. (*From* Cousins MJ, Bridenbaugh PO: Neural Blockade. Philadelphia, JB Lippincott, 1980, p 464; with permission.)

Melzack and Wall,[36] and the concept of endorphin release, have been suggested as possible explanations for its analgesic action. Although transcutaneous electrical nerve stimulation does not produce analgesia reliably and consistently during labor, it is more effective than a placebo in most women.

Inhalational Analgesia

Inhalational analgesia is frequently used in many countries in spite of the increased popularity of regional analgesic techniques. It employs subanesthetic concentrations of an inhaled gas or volatile agent, during labor. It is generally self-administered during the contractions, but may be administered by an anesthetist. The patient remains awake and retains her protective laryngeal reflexes. This technique should not be confused with inhalational anesthesia, which produces loss of consciousness.

Inhalational analgesia provides an unpredictable degree of pain relief. In many parturients the analgesia is satisfactory and provides an acceptable alternative to regional analgesia. Most of the inhalational anesthetic agents have been employed in this technique, but nitrous oxide has become the most commonly used inhalational analgesic. Several types of apparatus are available for self-administration. Nitrous oxide is usually mixed with oxygen, in a preset concentration, as it passes through a blender (Fig. 2); or is supplied from a prefilled cylinder containing the desired nitrous oxide/oxygen mixture. Generally, a 50% concentration is favored. In some cases a gas-scavenging device may be attached to the apparatus, to reduce atmospheric contamination with nitrous oxide (Fig. 2). Volatile agents, such as methoxyflurane and trichlorethylene, may be administered via specific vaporizers, but are not as widely used as nitrous oxide.

Systemic Medication

Parenterally administered analgesics during labor generally fall into three categories: (1) narcotics, (2) sedatives and tranquilizers, and (3) ketamine.

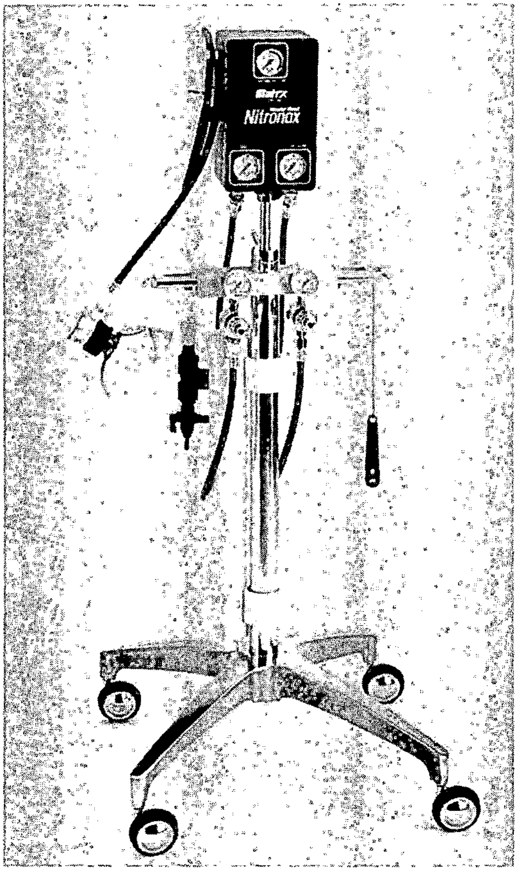


Figure 2. Nitrous oxide/oxygen apparatus for self-administered inhalation analgesia. Note the wide-bore tubing for waste-gas scavenging. (Courtesy of Matrix Medical Inc, Orchard Park, NY.)

Narcotics

Narcotics are the most effective parenterally administered analgesics, but they all produce dose-related respiratory depression and peripheral vasodilatation. Consequently, complete analgesia cannot be provided by these drugs without also producing maternal and neonatal hypoventilation and orthostatic hypotension. These large doses may also produce sedation, as well as obtundation of the protective laryngeal reflexes and some inhibition of uterine activity. All narcotics cross the placenta rapidly, and fetal depression is manifested by loss of beat-to-beat variability in the fetal heart rate pattern.

Narcotics may be administered by intermittent injection, continuous intravenous drip infusion, or by means of a patient-controlled demand apparatus. The latter consists of a prefilled syringe attached to a pump system that permits the patient to deliver to herself a small, predetermined, intravenous dose of the drug. A timing mechanism allows for a preset minimum time between injections and a maximum hourly dose.

Meperidine. Meperidine is the most frequently used narcotic in parturients. The peak effect is seen in 40 to 50 minutes after intramuscular injection and in 5 to 10 minutes after intravenous administration. The duration of analgesic action is 3 to 4 hours. Placental transmission is rapid, reaching the fetal circulation in 90 seconds after maternal intravenous injection.[56] Shnider and Moya[54] found a significant increase in the number of infants with low Apgar scores at birth, 2 hours after mothers had received intramuscular injections of meperidine.

Kuhnert et al[26, 27] have shown that metabolites of meperidine, notably normeperidine, increase in the fetus and neonate with time after administration of the drug to the mother; normeperidine reaches its highest levels in fetal tissues with longer drug-to-delivery intervals, and there is an increase in neonatal effects with the longer injection-to-delivery intervals.

Morphine. Morphine has a delayed onset and prolonged duration of action, compared with meperidine, and is seldom used as an analgesic during labor.

Fentanyl. Fentanyl is a potent narcotic with a rapid onset and short duration of action. The usual doses are 50 to 100 μg intramuscularly and 25 to 50 μg intravenously. Experience with this drug as the sole analgesic during labor is limited.

Agonist-Antagonist Narcotics. These are synthetic drugs having both opioid agonistic and weak antagonistic actions. Two of the newer members of this group of drugs are butorphanol and nalbuphine. In doses of 2 mg of butorphanol and 10 mg of nalbuphine they produce analgesia and respiratory depression, equivalent to 10 mg of morphine. However, they reach a ceiling effect and increasing doses do not produce further increase in respiratory depression.[16] Larger doses produce somnolence, which is generally undesirable in labor. They appear to offer no real advantage over meperidine.

Sedatives and Tranquilizers

Psychological preparation for labor will tend to allay fear and anxiety. Sometimes this is inadequate and pharmacologic reduction of anxiety is required. These drugs also promote sleep that may be beneficial in early labor.

Barbiturates. Barbiturates are not advisable during labor. They cross the placenta readily and have prolonged effects on the neonate.[22]

Phenothiazines. The phenothiazine derivatives are used for their sedative and anxiolytic properties. They are also potent antiemetics. The commonly used phenothiazines in obstetric practice are promethazine, propiomazine, and promazine. The latter, because of its greater α-adrenergic blocking properties, tends to cause hypotension.

Benzodiazepines. This group of drugs may be used in labor to provide sedation, to reduce the narcotic requirements, and as anticonvulsants. They cross the placenta rapidly, achieving cord drug levels similar to maternal plasma (diazepam may even exceed maternal levels).

Diazepam produces minimal fetal and neonatal effects when administered during labor in small doses (5–10 mg),[53] except for decreased beat-to-beat variability on the fetal heart rate tracing. When the total dose administered to the mother exceeds 30 mg, the drug and its metabolites persist in the neonate for days,[13] producing hypotonia, hypoactivity, poor sucking reflex, and hypothermia.[13, 14]

Lorazepam has a shorter duration of action than diazepam. The usual dose during labor is 1 to 2 mg sublingually or intravenously. Adverse neonatal effects have been reported, including low Apgar scores, hypothermia, poor sucking, and respiratory depression.[34, 59]

Ketamine

Low-dose (0.2–0.4 mg/kg) ketamine has been used to provide a brief period of analgesia and amnesia at delivery.[2] Higher doses (1 mg/kg) are used for induction of general anesthesia. Uterine blood flow and neonatal status are not affected by doses less than 1 mg/kg, but higher doses may cause low Apgar scores and neonatal hypotonia.[31]

Regional Analgesia

Regional analgesic techniques are the most commonly used methods of pain relief in obstetrics. They allow the parturient to remain alert and participate in the birth process. Fetal and neonatal effects are less marked than those produced by parenterally administered drugs.

Principles

1. Regional analgesia requires special skills on the part of both medical and nursing personnel, including the ability to recognize and treat complications.

2. An intravenous infusion of a crystalloid solution, through a large-bore indwelling cannula, must be established before administering any block.

3. Equipment for treating complications must be immediately available. This includes an oxygen delivery system, mask and bag, laryngoscope and a selection of endotracheal tubes, suction apparatus, and drugs for emergency induction of general anesthesia and treatment of hypotension.

Lumbar Epidural Analgesia

This is the most frequently employed form of regional analgesia during labor. Provided careful attention is paid to the dose and method of administration of the local anesthetic, the parturient is pain free, but has minimal, or no, motor block, there is no hypotension, and uterine contraction is not inhibited.

An intravenous infusion of at least 500 mL of a crystalloid solution must precede establishment of the block. This will decrease the incidence of hypotension associated with the sympathetic block that accompanies epidural analgesia. The loss of the vasoconstrictive response to hypotension, in the lower limbs, inhibits the ability to compensate for the decrease in blood pressure that results from intra-abdominal compression of the vena cava. This hypotension, along with reduced blood flow to the lower body from compression of the abdominal aorta, will reduce uteroplacental perfusion. In addition to the fluid preload, prevention of aortocaval compression is essential. This is best accomplished by avoiding the supine position and keeping the parturient lying on her side or sitting.

After the epidural catheter is inserted, preferably at the L3–4 or L2–3 level (Fig. 3), an initial test dose of the local anesthetic is injected. This is to enable recognition of accidental dural puncture or intravascular placement of the catheter. Addition of a vasoactive drug, such as epinephrine, is designed to indicate intravascular injection of the drug, while the small dose of local anesthetic (usually 3 mL) will reveal an inappropriate spinal block due to penetration of the dura by the epidural catheter. The value of this test dose is controversial. The dose of epinephrine used (usually 15 μg) will not invariably produce the telltale tachycardia. Unless an electrocardiogram or a pulse oximeter is attached to the patient, a transient increase in heart rate might be missed. Additionally, the stress of labor and the associated pain frequently cause a marked tachycardia, making interpretation of the efficacy of the test dose difficult. The author feels that the usual test dose administered is a more reliable indicator of subarachnoid, than intravascular, placement of the epidural catheter.

The 15 μg of epinephrine, usually employed in the test dose, may produce a transient decrease in uterine artery blood flow.[20] This is probably not of significance in uncomplicated term labor, as it approximates the reduction of blood flow that accompanies each contraction.

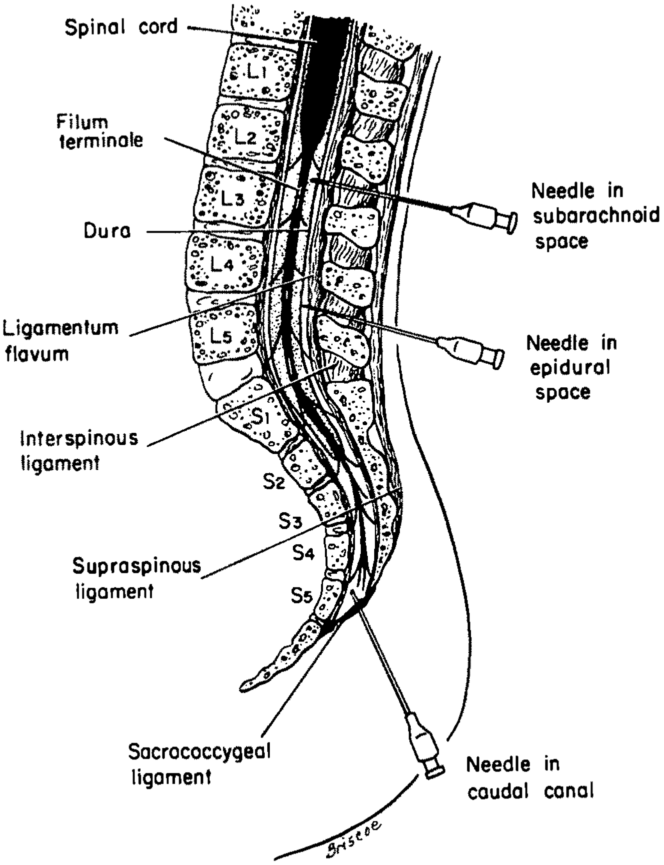


Figure 3. Diagram of lumbosacral anatomy showing needle placement for subarachnoid, lumbar epidural, and caudal blocks (*From* Shnider SM, Levinsons G (eds): Anaesthesia for Obstetrics, ed 2. Baltimore, Williams & Wilkins, 1987; with permission.)

It may be of significance in premature labor or in the presence of a compromised fetus.

The author's practice is to regard every injection of local anesthetic as a test dose. An initial amount of 3 to 4 mL of the local anesthetic (usually without epinephrine, during labor) is injected through the needle before insertion of the epidural catheter. After the catheter is securely taped in place, the woman is turned to her other side and the remainder of the analgesic dose is injected, usually another 4 to 5 mL. Subsequent top-up injections are always administered in divided doses of 4 to 5 mL, about 60 seconds apart. The low concentration of local anesthetic used during labor, administered in small divided doses, is not likely to cause a toxic reaction after intravenous injection or a total spinal block if injected into the subarachnoid space.

After each dose of local anesthetic, keep the mother on her side and monitor the blood pressure every 2 minutes for the first 10 minutes and then every 10 to 15 minutes. If hypotension occurs (blood pressure decreases 20% below base level or below 100 mm Hg systolic), ensure uterine displacement by turning the patient onto her side, lower the head of the bed, rapidly increase the rate of the intravenous infusion, and administer oxygen by mask. If the blood pressure does not respond to these measures within 1 to 2 minutes, inject 5 to 10 mg of ephedrine through the intravenous tubing. Repeat the ephedrine injection as necessary. The fetal heart rate is monitored continuously, preferably by an electronic monitor, whenever an epidural analgesic is administered.

Choice of Local Anesthetic. The local anesthetic used during labor should provide adequate analgesia, with a minimum of motor block. This will allow the mother to participate in the birth, while the minimal muscle relaxation will enhance normal flexion and internal rotation of the fetal head during the second stage of labor. The agents most commonly used are bupivacaine, lidocaine, and 2-chloroprocaine.

Bupivacaine is a long-acting amide local anesthetic. It provides excellent sensory analgesia with minimal motor block, when used in low concentration. During labor it is effective in concentrations of 0.125% to 0.25%. It is effective in a concentration as low as 0.0625% when combined with fentanyl, 1 to 3 μg/mL.[9] Bupivacaine has been stated to be more cardiotoxic than other amide local anesthetics, such as lidocaine.[4] Human[38, 40] and animal[10, 24, 50] studies have indicated that, at equivalent anesthetic concentrations, bupivacaine is about four times more cardiotoxic than lidocaine, and this toxicity is enhanced by severe hypoxia and acidosis.

Most of the reported cases of cardiac arrest have followed the use of 0.75% bupivacaine, and this concentration is not recommended in obstetric anesthesia practice. The low concentrations used during labor have not been associated with cardiotoxicity. However, the accidental intravascular injection of a large dose of local anesthetic, regardless of the concentration, must be carefully avoided. The author feels strongly that there is no justification for injection of a large bolus of local anesthetic through the epidural catheter. Incremental injection of small boluses, no larger than 5 mL, until the required effect is obtained, is a safe technique.

Lidocaine has a shorter duration of action than bupivacaine and is less frequently used to provide epidural analgesia during labor. It has a more rapid onset of action and is frequently the agent of choice when anesthesia, rather than analgesia, is required. Lidocaine 2%, or carbonated lidocaine where available, with the addition of 1:400,000 or 1:200,000 epinephrine (2.5–5.0 μg/mL) will provide rapid and adequate anesthesia for instrumental or operative delivery.

2-Chloroprocaine, an ester local anesthetic, has a rapid onset and short duration of action. For epidural analgesia during labor, it is best used as a continuous infusion in a concentration of 0.5%. The drug is rapidly hydrolyzed by plasma pseudocholinesterase, with a maternal half-life of 21 seconds.[25, 44] Consequently, it has low toxicity and little drug crosses the placenta.

Several case reports were published of prolonged neurologic damage, following accidental subarachnoid injection of large volumes of 2-chloroprocaine.[39, 45, 46] Subsequent animal studies indicated that the likely cause was a combination of a low pH with a high sodium bisulfite (added as an antioxidant) concentration.[18, 58]

Although commercial preparations of chloroprocaine, for epidural use, no longer contain bisulfite (at least in the United States; Canadian supplies still contain 0.7 mg of bisulfite per milliliter), if a large volume of the drug is accidently injected intrathecally, the recommendation is to aspirate as much of the CSF (containing the drug) as possible, replacing it with saline. Other measures to support ventilation and blood pressure must be instituted rapidly.

Ropivacaine is a new long-acting amide local anesthetic, now undergoing clinical trials. It is structurally related to bupivacaine and mepivacaine. Studies in animals[3, 5, 51] and human volunteers[52] have indicated that ropivacaine has lower CNS and cardiac toxicity than bupivacaine. Studies of its use in epidural anesthesia[12] have shown that ropivacaine produces less motor block than equal concentrations of bupivacaine. This drug shows promise of becoming a useful agent for epidural analgesia during labor, but further clinical studies are necessary, especially to assess its fetal and neonatal effects.

Management. Epidural analgesia may be managed in a variety of ways, depending on the choice of the anesthesiologist, experience, and local facilities.

Intermittent Injection. This is the conventional and perhaps the most frequently employed technique. After the block has been established, often with 6 to 10 mL of 0.25% bupivacaine, further doses are administered as required to maintain analgesia. Generally, this will be at the request of the parturient as she is aware of returning pain.

Bupivacaine is the most commonly used drug for this technique. Either 0.125% or 0.25% concentrations are used, depending on the individual needs of the parturients. The addition of 1:800,000 epinephrine to 0.125% bupivacaine will intensify the block.

Continuous Infusion. Continuous infusion of low concentrations of local anesthetic into the epidural space will provide consistent analgesia, without the fluctuations that are part of the intermittent injection technique. After the block has been established, often with 0.25% bupivacaine, an infusion of 0.125% bupivacaine may be administered through a constant rate infusion pump. The rate is set at about 8 to 10 mL/h and adjusted according to the needs of the patient. An addition of fentanyl, 1 to 3 μg/mL, will provide excellent analgesia while reducing the local anesthetic requirement. Chestnut et al[9] have reported that the addition of fentanyl to the local anesthetic will allow the concentration of bupivacaine to be lowered to 0.0625%. This will markedly reduce the total amount of local anesthetic administered, as well as decrease the incidence of hypotension or motor block. Other lipid-soluble narcotics, such as alfentanil and sufentanil, appear to offer no advantage over fentanyl, and the latter is the most frequently used narcotic in epidural analgesia.

The segmental level of the block must be constantly monitored. If it rises above T8 the rate of the infusion must be reduced (or stopped). Although observation by skilled nurses is important, the anesthesiologist must make frequent visits and assessments of the block. The possible complications are intravascular or intrathecal migration of the epidural catheter. Migration into a blood vessel may be recognized by loss of analgesia. The slow rate of flow avoids the risk of sudden toxic manifestations. Intrathecal migration will be followed by slow development of a motor block. Ascending sensory block will be too slow to be recognized immediately.

Patient-Controlled Epidural Analgesia. Recently, the concept of allowing the parturient to control the timing of her epidural injections has received attention.[17, 33] After the loading dose has established adequate analgesia, the patient-controlled analgesia apparatus is connected to the epidural catheter and the parturient is instructed in its use. The local anesthetic solution (with or without the addition of a lipid-soluble narcotic) used for maintenance is the same as described previously for intermittent injection or continuous infusion.

The drug may be administered on demand by the parturient or it may be provided as a slow background infusion, with the parturient able to give herself additional boluses as needed. In either case the anesthesiologist will set the bolus dose, lockout time, and maximum hourly dose. Regular visits, as for continuous infusion technique, must be made to assess the height of the block, adequacy of analgesia, and onset of complications. Patient-controlled epidural anesthesia may require a lower total dose of local anesthetic, and patient satisfaction is generally greater than with the intermittent top-up technique.

Contraindications to Epidural Analgesia. Absolute contraindications include patient refusal, uncorrected hypovolemia, local infection, and coagulopathies. Epidural analgesia in women who are receiving prophylactic heparin and aspirin is controversial. Many anesthesiologists no longer consider this to be an absolute contraindication, but will assess each case individually, after obtaining the platelet count, prothrombin time, partial thromboplastin time, and, if indicated, bleeding time. Neurologic disease does not necessarily contraindicate epidural analgesia. The relative risks and benefits must be assessed in each individual.

Paracervical Block

This block involves injection of local anesthetic into the tissues on either side of the cervix. It provides good analgesia for the first stage of labor, but the site of injection carries a high risk of intravascular injection of local anesthetic. The lower segment is thin and direct injection into the fetal scalp is possible. Reports of severe fetal bradycardia and even fetal death, associated with this block, have led to its infrequent use.

Pudendal Block

This block will provide anesthesia of the perineum and is usually administered by the obstetrician. It is useful for repair of an episiotomy or for low forceps. It is inadequate for a midforceps delivery.

Complications of Regional Analgesia

Hypotension. This is the most common complication of regional blockade. It is associated with sympathetic block, and its severity is related to the segmental height of the block, whether an adequate fluid preload has been administered, and effective lateral uterine displacement.

Treatment consists of rapid intravenous infusion, lowering the head of the bed, left uterine displacement, and oxygen by face mask. If these measures do not restore the blood pressure to a normal level within 1 to 2 minutes, ephedrine, 5 to 10 mg, is injected intravenously and repeated if necessary.

Total Spinal Anesthesia. This is caused by excessively high spread of local anesthetic. The most common cause is unrecognized accidental dural puncture, during insertion of an epidural needle or catheter. Apnea, hypotension, and loss of consciousness develop rapidly.

Treatment consists of establishing an airway, ventilation, and restoring the blood pressure. Equipment and drugs for resuscitation must always be readily available whenever regional blockade is performed. Run the intravenous infusion rapidly. Immediate endotracheal intubation protects the airway from aspiration of regurgitated gastric contents and also allows efficient ventilation with oxygen. Lower the head of the table and ensure adequate left uterine displacement. Ephedrine is the drug of choice for treatment of hypotension in intravenous doses of 5 to 15 mg, repeated as required. If the distal end of the epidural catheter is in the subarachnoid space, CSF may be aspirated to remove the local anesthetic.

Convulsions. CNS toxicity results from excessively high blood levels of local anesthetic. This may follow overdosage or, more commonly, accidental intravascular injection of the drug. Early signs of toxicity, if recognized, are treated by intravenous injection of 50 to 100 mg of thiopental or 5 mg of diazepam and oxygen by face mask. Convulsions are associated with rapid development of acidosis and anoxia. Ventilation must be immediately established. Endotracheal intubation is facilitated by intravenous injection of 60 to 80 mg of succinylcholine. Monitor the blood pressure and treat hypotension immediately with a vasopressor. If the convulsion is rapidly and adequately treated, uterine blood flow will be restored and the fetus will recover.

Neurologic Injury. Direct neurologic complications of regional analgesia are rare. Paresthesia on insertion of the needle or catheter indicate pressure on a nerve root. Withdraw the needle immediately and reenter the epidural space at another level. Hematoma or abscess in the epidural space is rare. Hematoma may be associated with a bleeding or clotting disorder. Most nerve injuries in obstetric practice are not related to regional blocks, but are due to compression of the sacral plexus by the fetal head or damage to peripheral nerves by the lithotomy position.

Postdural Puncture Headache. The incidence of accidental dural puncture should be low (<1%). However, the hole made by the large epidural needle, as well as the Valsalva maneuvers during delivery, predispose to leakage of CSF in sufficient quantity to cause headache in many of these people.

Conservative treatment consists of bed rest, analgesics, and hydration. A tight abdominal binder has been recommended to increase epidural pressure. Epidural saline injections have also been advocated, but the success rate is disappointing. Epidural blood patch, using autologous venous blood, is the recommended treatment for severe headache. Under rigid aseptic conditions, the epidural space is entered with a needle at the level of the dural puncture. About 15 mL of venous blood is withdrawn from an accessible vein (usually the antecubital vein) and immediately injected, slowly, into the epidural space. The success rate is about 95%. Prophylactic epidural blood patch is controversial. After the block has worn off, 15 to 20 mL of autologous venous blood may be injected through the epidural catheter. Reports of the efficacy of this procedure are contradictory.[8, 11, 32]

Spinal Narcotics

Reference has been made (vide supra) to the use of short-acting lipid-soluble narcotics as adjuvants to local anesthetics in the epidural space during labor. Epidural narcotics alone do not produce either motor or sympathetic block, but they have not been proved to provide adequate analgesia during labor.[7, 21]

Intrathecal morphine, in doses of 0.5 to 1.0 mg, does provide effective analgesia for first-stage labor,[1] but the side effects (pruritus, nausea, vomiting, drowsiness, respiratory depression) were reported to be troublesome. Morphine has a slow onset of action and the addition of a small dose of fentanyl will provide a more rapid onset of analgesia, to supplement the long duration of the morphine. In patients with heart disease, when it is important to avoid hypotension, intrathecal narcotics may be a useful alternative to epidural analgesia.

Spinal narcotics are effective in the prevention of pain after cesarean section. Epidural morphine has been proved to provide effective analgesia for about 24 hours.[15, 23, 49] Side effects are common, but are easily treated if troublesome. Reducing the dose of morphine to 3 mg does not shorten the duration of action, but does lessen the incidence and severity of side effects.[15] The lipid-soluble narcotics, fentanil and sufentanil, have been shown to provide good epidural analgesia, but the duration is short (3–5 hours).[35, 43, 47, 48] They may be repeated, if the epidural catheter is left in place, but offer no advantage over epidural morphine.

Intrathecal morphine, 0.25 mg, may be administered when the cesarean section is done under subarachnoid block. It is injected with the local anesthetic and may be combined with 6 to 10 μg of fentanyl if a more rapid onset of action is desired.

The incidence of delayed respiratory depression is lower in parturients than in the general population.[15] They are generally young and healthy, and the increased progesterone secretion possibly raises the sensitivity of the respiratory center to carbon dioxide.

References

1. Abboud TK, Shnider SM, Dailey PA, et al: Hyperbaric intrathecal morphine for the relief of labour pain. Anesthesiology 57:A384, 1982
2. Akamatsu TJ, Bonica JJ, Rehmet R, et al: Experiences with the use of ketamine for parturition. 1. Primary anesthetic for vaginal delivery. Anesth Analg 53:284, 1974
3. Akerman B, Hellberg I, Trossvik C: Primary evaluation of the local anaesthetic properties of the amino agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 32:571, 1988
4. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine [editorial]. Anesthesiology 51:285, 1979
5. Arthur G, Feldman HS, Covino BC: Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anaesthetic. Anesth Analg 67:1053, 1988
6. Bonica JJ. Pain of parturition. Anesthesiol Clin North Am 4:1, 1986
7. Carrie LES, O'Sullivan GM, Seegobin R: Epidural fentanyl in labour. Anaesthesia 36:965, 1981
8. Cheek TG, Banner R, Sauter J, et al: Prophylactic epidural blood patch is effective. Br J Anaesth 61:340, 1988
9. Chestnut DH, Owen CL, Bates JN, et al: Continuous infusion epidural analgesia during labor: A randomised double-blind comparison of 0.0625% bupivacaine/0.0002% fentanyl versus 0.125% bupivacaine. Anesthesiology 68:754, 1988
10. Clarkson CW, Hondeghem LM: Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 62:396, 1985
11. Colonna-Romano P, Shapiro BC: Prophylactic epidural blood patch in obstetrics. Anesthesiology 69:A665, 1988
12. Concepcion M, Arthur RG, Steele SM, et al: A new local anesthetic, ropivacaine. Its epidural effects in humans. Anesth Analg 70:80, 1990
13. Cree JE, Meyer J, Hailey DM: Diazepam in labor: Its metabolism and effect on the clinical condition and thermogenesis of the newborn. Br Med J 4:251, 1973
14. Flowers CE, Rudolph AG, Desmond MM: Diazepam (Valium) as an adjunct in obstetric analgesia. Obstet Gynecol 34:68, 1969
15. Fuller JG, McMorland GH, Douglas MJ, et al: Epidural morphine for analgesia after Caesarean section: A report of 4880 patients. Can J Anaesth 37:636, 1990
16. Gal TJ: Analgesic and respiratory depressant activity of nalbuphine: A comparison with morphine. Anesthesiology 55:367, 1982
17. Gambling DR, McMorland GH, YU P, et al: Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. Anesth Analg 70:256, 1990
18. Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy. II. Is chloroprocaine neurotoxic. Reg Anesth 9:135, 1984
19. Hagerdal M, Morgan CW, Sumner AE, et al: Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 59:425, 1983

20. Hood DD, Dewan DM, James FM: Maternal and fetal effects of epinephrine in gravid ewes. Anesthesiology 64:610, 1986
21. Hughes SC, Rosen MA, Shnider SM, et al: Maternal and neonatal effects of epidural morphine for labor and delivery. Anesth Analg 63:319, 1984
22. Irving FC: Advantages and disadvantages of barbiturates in obstetrics. RI Med J 28:493, 1945
23. Kotelko DM, Dailey PA, Shnider SM, et al: Epidural morphine analgesia after cesarean delivery. Obstet Gynecol 63:409, 1984
24. Kotelko DM, Shnider SM, Dailey PA, et al: Bupivacaine-induced cardiac arrythmias in sheep. Anesthesiology 60:10, 1984
25. Kuhnert BR, Kuhnert PM, Prochaska BS, et al: Plasma levels of 2-chloroprocaine in obstetric patients and their neonates after epidural anesthesia. Anesthesiology 53:21, 1980
26. Kuhnert BR, Kuhnert PM, Tu AL, et al: Meperidine and normeperidine levels following meperidine administration during labor. II. Fetus and neonate. Am J Obstet Gynecol 133:907, 1971
27. Kuhnert BR, Linn PL, Kennard MJ, et al: Effects of low dosses of meperidine on neonatal behavior. Anesth Analg 64:335, 1985
28. Lederman E, Lederman RP, Work BA, et al: Maternal psychological and physiological correlates of fetal-newborn health status. Am J Obstst Gynecol 139:956, 1981
29. Lederman RP, Lederman E, Work BA, et al: The relationship of maternal anxiety, plasma catecholamines and plasma cortisol to progress in labor. Am J Obstet Gynecol 132:495, 1978
30. Lederman RP, McCann DS, Work BA, et al: Endogenous plasma epinephrine and norepinephrine in last-trimester pregnancy and labor. Am J Obstet Gynecol 129:5, 1977
31. Little B, Chang T, Chueot L, et al: Study of ketamine as an obstetric agent. Am J Obstet Gynecol 113:247, 1972
32. Loser EA, Hill GE, Bennett GM, et al: Time vs. success rate for epidural blood patch. Anesthesiology 49:147, 1978
33. Lysak SZ, Eisenach JC, Dobson CE: Patient controlled analgesia during labor: A comparison of three solutions with a continuous infusion control. Anesthesiology 72:44, 1990
34. McAuley DM, O'Neill MP, Moore J, et al: Lorazepam premedication for labour. Br J Obstet Gynaecol 89:149, 1982
35. McMorland GH, Douglas MJ, Kim J, et al: Epidural sufentanil for post-Caesarean section analgesia. Can J Anaesth 37:432, 1990
36. Melzack R, Wall PD: Pain mechanism: A new theory. Science 150:971, 1965
37. Melzack R, Taenzer P, Feldman P, et al: Labour is still painful after prepared childbirth training. Can Med Assoc J 125:357, 1981
38. Moore DC, Crawford RD, Scurlock JE: Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 53:259, 1980
39. Moore DC, Speirdijk J, Van Kleef JD, et al: Chloroprocaine neurotoxicity: Four additional cases. Anesth Analg 61:155, 1982
40. Moore DC, Thomson GE, Crawford RD: Long-acting local anesthetic drugs and convulsions with hypoxia and acidosis. Anesthesiology 56:230, 1982
41. Morishima HO, Yeh MN, James LS: Reduced uterine blood flow and fetal hypoxemia with acute maternal distress: Experimental observations in pregnant baboon. Am J Obstet Gynecol 134:270, 1979
42. Myers RE, Myers SE: Use of sedative, analgesic and anesthetic drugs during labor and delivery: Bane or boon? Am J Obstet Gynecol 133:83, 1979
43. Naulty JS, Datta S, Ostheimer GW, et al: Epidural fentanyl for postcesarean delivery pain management. Anesthesiology 63:694, 1985
44. O'Brien JE, Abbey V, Huisvark O: Metabolism and measurement of 2-chloroprocaine, an ester-type local anesthetic. J Pharm Sci 68:75, 1979
45. Ravindran RS, Bond VK, Tasch MD, et al: Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 59:447, 1980
46. Reisner LS, Hochman BN, Plumer MH: Persistent neurological deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine. Anesth Analg 59:452, 1980

47. Robertson K, Douglas MJ, McMorland GH: Epidural fentanyl, with and without epinephrine, for post-Caesarean section analgesia. Can Anaesth Soc J 32:502, 1985
48. Rosen MA, Dailey PA, Hughes SC, et al: Epidural sufentanil for postoperative analgesia after cesarean section. Anesthesiology 68:448, 1988
49. Rosen MA, Hughes SC, Shnider SM, et al: Epidural morphine for the relief of postoperative pain after cesarean delivery. Anesth Analg 62:666, 1983
50. Rosen MA, Thigpen JW, Shnider SM, et al: Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 64:1089, 1985
51. Rutten AJ, Nancarrow C, Mather LE, et al: Hemodynamic and central nervous system effects of lidocaine, bupivacaine and ropivacaine in sheep. Anesth Analg 69:291, 1989
52. Scott DB, Lee A, Fagan D, et al: Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 69:563, 1989
53. Sher J, Hailey DM, Beard RW: The effect of diazepam on the fetus. J Obstet Gynaecol Br Commonw (Br J Obstet Gynaecol) 79:635, 1972
54. Shnider SM, Moya F: Effects of meperidine on the newborn infant. Am J Obstet Gynecol 89:1009, 1964
55. Shnider SM, Abboud TK, Artal R, et al: Maternal catecholamines decrease during labor after lumbar epidural anesthesia. Am J Obstet Gynecol 147:13, 1983
56. Shnider SM, Way EL, Lord MJ: Rate of appearance and disappearance of meperidine in fetal blood after administration of narcotic to the mother. Anesthesiology 27:227, 1966
57. Shnider SM, Wright RG, Levinson G, et al: Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology 50:524, 1979
58. Wang BC, Hillman DE, Spielholz NI, et al: Chronic neurological deficits and Nesacaine-CE. An effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfite? Anesth Analg 63:445, 1984
59. Whitelaw AGL, Cummings AJ, McFadyen IR: Effect of maternal lorazepam on the neonate. Br Med J 282:1106, 1981

Address reprint requests to

Graham H. McMorland, MB, ChB, DA, FRCPC
Department of Anaesthesia
Grace Hospital
4490 Oak Street
Vancouver, B.C.
V4K 4R7 Canada

MANAGEMENT OF PAIN IN INTENSIVE CARE SETTINGS

Donald S. Stevens, MD, and W. Thomas Edwards, PhD, MD

Pain is common in critically ill patients.[38, 45, 54] In fact, as can be seen in Table 1, patient reports about pain management are unchanged from 25 to 30 years ago. Ineffective analgesia in intensive care settings is likely more related to the manner in which analgesics are used than to the nature or properties of the analgesics themselves. Advanced pain management techniques are currently available that can provide much improved pain relief, as well as improved patient outcomes.

Pain experienced by patients in intensive care units has frequently been undertreated because of fears of depressing spontaneous ventilation, inducing narcotic dependence, inducing cardiovascular instability, or masking underlying surgical pathology in a critically ill patient. The analgesic treatment plan in essence rests on attitudes formed in both physicians and nurses early in their medical training. Education in pain management may be the single most important tool for improving patient comfort.[52]

In order to understand the concepts of pain management, several definitions are in order. *Pain* is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[58] *Suffering* is the reaction of an organism to the experience of pain.[23] *Pain-related behavior* is behavior that leads an observer to conclude that pain and suffering are being experienced.[23] The relationship among the components of acute pain is shown in Figure 1. The observer cannot tell the relative sizes of the circles because all that can be seen is the "pain-related behavior." It is common to see two patients who have undergone similar operations

---

From the Department of Anesthesiology, University of Massachusetts Medical Center, Worcester, Massachusetts; and Department of Anesthesiology, University of Washington–Harborview Medical Center, Seattle, Washington

Table 1. INCIDENCE OF THERAPEUTIC FAILURES WHEN CONVENTIONAL INTRAMUSCULAR INJECTIONS OF OPIOIDS ARE GIVEN FOR POSTOPERATIVE PAIN RELIEF

Reference	No. of Patients	Insufficient Analgesia Moderate or Severe Pain (%)
Papper et al (1952)	286	33
Lasagna and Beecher (1954)	122	33
Keats (1965)	?	26–53
Keeri-Szanto and Heaman (1972)	106	20
Cronin et al (1973)	100	42
Banister (1974)	437	12–26
Tammisto (1978)	100	24
Cohen (1980)	109	75
Tamsen et al (1982)	56	38
Donovan (1983)	200	31
Sriwatanakul et al (1983)	81	41

From Harmer M, Rosen M, Vickers MD: Patient Controlled Analgesia. Cambridge, Blackwell Scientific, 1985; with permission.

with similar anesthetics, one of whom seems to experience great pain while the other appears to have little pain. One important concept to remember is that pain is a totally subjective phenomenon. When the patient says "I hurt" it is true, regardless of whether the observer feels that the amount of pain reported is appropriate.

Nociception, which is the neurophysiologic antecedent of pain, as well as pain itself, are modulated by many things including ethnocultural backgrounds, learned behaviors, and the meaning of the particular experience for the individual.[2, 52] The most successful approach to treatment will take into consideration both pharmacologic and nonpharmacologic factors. Any approach that fails to account for individual

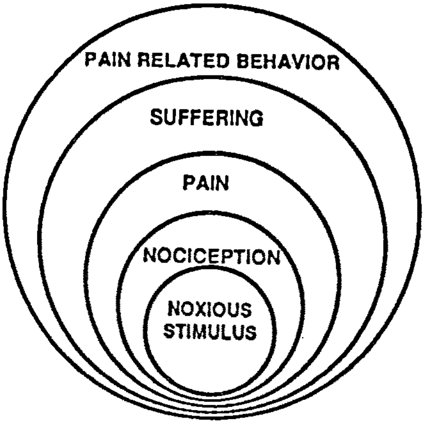


Figure 1. The multifaceted model of acute pain proposed by Edwards[22] as derived from the Multifaceted Model of Pain. (*From* Loeser JD: Concepts of pain. *In* Stanton-Hicks M, Boas R (eds): Chronic Low Back Pain. New York, Raven Press, 1982, p 124; with permission.)

patient variability in all aspects of the pain experience will not provide consistently positive outcomes.

FORMULATING A TREATMENT PLAN: QUESTIONS THAT NEED TO BE ASKED

The routine course of acute pain is to decrease gradually and to end in spontaneous remission. During different stages of the recovery process, the quality of the pain may also change. Therefore, it is important to ask several questions about the pain when one is designing a treatment plan.

Where Does It Hurt?

Is the location of the pain appropriate for the injury sustained or for the surgery performed, or is it in another location entirely? If nociception is not accounted for by the injury or by the surgical procedure, or by deep visceral or referred pain as applicable, then a secondary process must be investigated.

How Much Does It Hurt?

If possible, in the case of postoperative pain, quantification of pain should use a system that was taught before surgery. The visual[41] or verbal analogue scales are of use (Fig. 2), even when patients are intubated and ventilated, provided they can interact with the examiner. A numerical scale without the visual analogue also can be used

Five Point Global Scale	NONE=0 A LITTLE=1 SOME=2 A LOT=3 THE WORST=4
Verbal Quantitative	0 . . . . 5 . . . . 10 none worst imaginable
Visual Pain Analog Scale (VPAS)	no worst -- pain pain Place a mark on the line to show where your pain is now.

Figure 2. Techniques for grading pain before and after treatment. These scales can be useful for evaluating patient reports of pain.

effectively. Sensory and affective components of pain can be assessed using the short-form McGill Pain Questionnaire.[57] Patients also can be assessed even if they are unable to communicate. Various markers of sympathetic activity, such as restlessness, sweating, tachycardia, lacrimation, pupillary dilatation, and hypertension all can be graded as signs of pain intensity, although any one of there is not an adequate measure of pain intensity in itself.[71]

What Does It Feel Like?

If the pain is sharp, it is probably due to direct nociception, such as is associated with an incision. Dull aching sensations, well responsive to opioids, are typical of pain arising from deeper structures. A pulling or tugging sensation is in keeping with the stitches in the wound and with some visceral stimulation. Buzzing, stinging, pins and needles, or a sensation of electricity indicate abnormal neural function. These sensations are minimal and short-lived following regional anesthesia. When they occur in the postoperative or trauma setting, they are more indicative of neuronal dysfunction or reestablishment of neural function. Painful dysesthesias also may occur as part of a preexisting medical condition, as seen in peripheral neuropathies.

FORMULATING A TREATMENT PLAN: AN ANATOMIC APPROACH

The anatomy of the pain pathway is presented in schematic form in Figure 3. Each separate part of the pain pathway can be influenced so that the nociceptive signal is diminished or eliminated. This can be done in the *periphery*, at the *spinal cord level*, or by using a *systemic approach*.

SPECIFIC ANALGESIC TECHNIQUES: THE PERIPHERY

Nonsteroidal Anti-inflammatory Agents

These medications interfere with the production of the prostaglandins that can produce hyperalgesia.[26] Ketorolac has recently been introduced in the United States in parenteral formulation and is an effective analgesic.[34] Indomethacin suppositories (100 mg three times a day) also have been shown to reduce opioid needs in postthoracotomy patients in comparison with controls.[51]

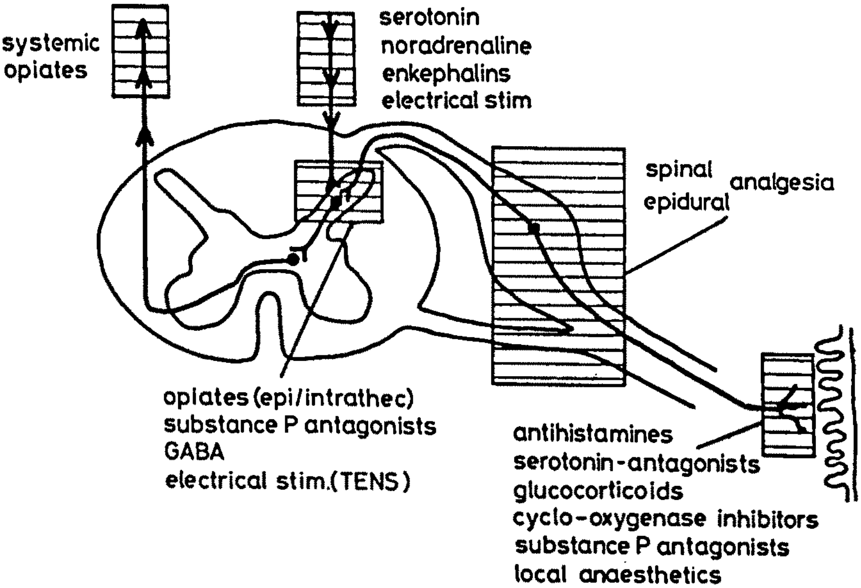


Figure 3. A map of the path of nociceptive information from the periphery to the central nervous system. (*From* Cousins MJ, Phillips GD: Acute Pain Management. New York, Churchill Livingstone, 1986, p 52; with permission.)

Local Anesthetic Techniques

Local Infiltration

The action of local anesthetics after local infiltration may decrease analgesic needs for several days.[93] One explanation may be that blockade of nociceptive afferent impulses prevents an increase in the excitability of the neurons of the intraspinal pain pathway, preventing release of algogens.[100]

Intercostal Blocks

Repeated intermittent intercostal nerve blocks can be used to provide analgesia for thoracic injuries and for treatment of postoperative pain. This technique provides analgesia without widespread sympathetic blockade, weakness of major muscle groups, and sedation or respiratory depression.[25] Disadvantages include the need for repeated injections,[33] the risk of pneumothorax,[59] and possible systemic toxic reactions to the local anesthetic if excessive amounts are used. This technique may not be appropriate in anticoagulated patients because of the risk of bleeding and hematoma formation.[61] Intercostal nerve blocks can be performed under direct vision during a thoracotomy.[31] Because single intercostal blocks need to be repeated to provide long-lasting analgesia, a continuous technique has been developed for intercostal nerve block.[63]

Treatment with an intercostal block technique is most appropriate for the treatment of unilateral thoracic or upper abdominal pain. A patient with an ineffective cough due to pain from fractured ribs would be a good candidate.

Paravertebral Block

Analgesia for pain in the thorax or abdomen can be provided by a paravertebral nerve block. This can be performed either as a single injection of local anesthetic or as a continuous catheter technique.[21] Injection into a paravertebral catheter appears to cause flow laterally into an intercostal space and also up and down the paravertebral space ipsilaterally. This allows several intercostal nerves to be bathed with anesthetic and gives analgesia over several dermatomal levels.[15] The advantages of paravertebral block are similar to those found with an intercostal technique. Risks of this technique include pneumothorax, epidural blockade, and inaccurate catheter placement.[66]

Interpleural Analgesia

Interpleural regional analgesia was originally described as a continuous catheter technique.[76] Needle placement is similar to that used for thoracentesis, with the bevel of the needle directed cephalad. Entry into the interpleural space is detected by having attached to the needle a well-lubricated glass syringe containing air. Because pressure in the interpleural space is below atmospheric pressure (often called negative pressure), the plunger of the syringe is drawn inward when the parietal pleura is crossed. Alternative methods for placement include use of a "hanging drop" technique, in which the negative pressure on entry into the interpleural space is recognized when the drop is sucked inward,[84] or positioning a catheter in the interpleural space under direct vision during thoracotomy.[47] Either intermittent injections or a continuous infusion of local anesthetic may be used. Care must be exercised with the use of a continuous infusion to avoid local anesthetic toxicity.

Interpleural analgesia has been used quite successfully to manage various types of pain in the thorax and upper abdomen, including pain after thoracotomy,[48] and for patients with multiple rib fractures.[77] How interpleural analgesia works is still uncertain. Possibilities include diffusion of local anesthetic through the parietal pleura either superficially to block the intercostal nerves or posteromedially to block nerve roots and sympathetic ganglia in the paravertebral space.[17, 67] There may possibly be direct local anesthetic action on pleural nerve endings.[67] Because the flow of fluid in the interpleural space is gravity dependent, placing the patient in the lateral decubitus position with the affected side upward before each dose may allow for a better block.[75]

There is one case report of a toxic serum level of bupivacaine following a single interpleural injection in a patient with a pleural effusion after pneumonia.[79] A recent thoracic infection with concomitant pleuritis should be considered a contraindication to the use of interpleural analgesia, because greater absorption of the local anesthetic than is usually seen may occur and may lead to toxic serum levels.[79] Fibrosis of the pleura, which may make it difficult to identify entry into the pleural space, also is a contraindication.

The greatest utility of this technique may be in circumstances that contraindicate the use of other regional analgesia techniques, such as when severe vertebral injuries are present with rib fractures.

Other Regional Blocks

Brachial plexus blocks, either by a single shot or continuous catheter technique, can provide hours of analgesia for vigorous turning in bed, chest physiotherapy, and other activities that would be limited by upper extremity pain.[32] Continuous femoral nerve block can be of benefit in patients who have localized knee or thigh pain, such as is seen with femur fractures.[40]

SPECIFIC ANALGESIC TECHNIQUES: SPINAL CORD LEVEL

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation may work to down-modulate the afferent nociceptive signal at the spinal cord level or possibly at the brain stem level.[64, 94] When transcutaneous electrical nerve stimulation is used alone, adequate analgesia may not be produced, but multiple studies have shown a definite benefit when transcutaneous electrical nerve stimulation is combined with other methods of analgesia for the treatment of acute pain problems. There also is a tendency toward a reduced frequency of nausea, vomiting, paralytic ileus, and atelectasis postoperatively in patients using transcutaneous electrical nerve stimulation.[42]

Central Conduction Block: Epidural or Subarachnoid

General Considerations

The transmission of afferent nociceptive information also may be altered at a central level by more invasive techniques. Afferent conduction can be blocked at the nerve root or spinal cord level with local anesthetics, or down-modulated centrally by intraspinal opioids acting on specific opiate receptors in the dorsal horn of the spinal cord.

Subarachnoid Techniques: Opioids

Single doses of intrathecal morphine or fentanyl have been given at the time of lumbar puncture to provide analgesia postoperatively for up to 24 hours. The use of a single intrathecal dose of morphine in a range of 3 to 7 μg/kg has been recommended for postoperative analgesia because of the ease and simplicity of its administration.[88] However, the limited duration of intrathecal morphine analgesia often makes continuous epidural opioid analgesia preferable.

Epidural Techniques: Catheter Placement

If a local anesthetic is to be used, the epidural catheter should be placed for a segmental block, at an interspace close to the center of the dermatomal segments needing analgesia. If morphine is to be used, a more caudad approach may be adequate, because rostral spread of morphine in the cerebrospinal fluid (CSF) will cover a more cephalad dermatomal site.[11, 30] More lipid-soluble opioids (such as fentanyl or sufentanil) should be given through a catheter placed as for segmental analgesia.

Epidural Techniques: Continuous Local Anesthetic

Analgesia can be provided by the continuous infusion of local anesthetics. It is recommended that an adequate initial level of analgesia be obtained before starting the continuous infusion. This can be accomplished by the use of 1% lidocaine or by the use of 0.25% bupivacaine.

The use of bupivacaine for continuous infusion is preferable, because of the relative sparing of motor function with this agent. A routine starting dose would be 6 to 8 mL/h of 0.125% bupivacaine (without epinephrine) administered by an infusion pump. Our usual protocol to deal with tachyphylaxis is to increase the infusion rate stepwise by 2 mL/h increments to a maximum of 14 to 16 mL/h. At the maximum volume, if there is inadequate analgesia, the bupivacaine concentration is increased to 0.25%, and the infusion rate slowed to 8 mL/h. Further escalation in bupivacaine dosage can be made as just described, first increasing the infusion rate. The maximum dose infused should not exceed 1.5 mg/kg/h, however, and each increase in infusion rate should be preceded by reinforcement of the block as at the outset so that adequate analgesia is obtained.

A continuous epidural infusion of local anesthetics allows prolonged analgesia,[35, 81] but hypotension secondary to sympathetic block can be frequently seen.[16, 43] Hypotension can usually be treated easily by infusion of an adequate volume of intravenous fluid,[35] or by infusion of a small dose of an α-adrenergic agent, such as phenylephrine.

Use of a continuous epidural infusion of local anesthetics for anesthesia and for postoperative analgesia has been associated with a reduction in postoperative complications in high-risk patients.[102] Other studies using thoracic epidural analgesia in patients with unstable angina pectoris[7] or acute myocardial infarction[91] indicate that hypotension does occur in almost every case, but that there is not an unfavorable effect on myocardial perfusion, even in these critically ill patients.

Epidural Techniques: Intermittent Dose Opioid

Epidural opioids are extremely effective in producing analgesia, because they are administered close to the dorsal horn of the spinal cord. Morphine is the opioid most commonly used. Morphine tends to stay dissolved in the CSF instead of being absorbed by the spinal cord structures or taken up into the circulation, because of its low lipid solubility. There is much more rostral migration of morphine than is seen with more lipid-soluble opioids such as fentanyl, which tends to be absorbed into lipid-containing structures close to the site of injection.

Dosing schedules should be dependent on the patient's response to the medication. A patient needing a second dose of epidural morphine about 6 hours after surgery is not uncommon. Breakthrough pain occurring before this may be treated by a small dose of epidural fentanyl and the next dose of epidural morphine adjusted upward by about 20%. Dosing every 8 hours may be needed for the first 1 to 2 days. Occasionally patients will need only one dose per day for good analgesia; this is particularly true for elderly patients. Timed reinjection (rather than as needed) is preferable, and the dosing interval usually can be determined within the first 24 hours. Tables 2 and 3 provide guidelines for dosing with the most commonly used intraspinal opioids, as well as suggestions for dose modification to account for patient age and catheter position.

Epidural catheters usually remain in place 2 to 3 days, but can be left in place indefinitely if there are no signs of inflammation and there is a need for continued aggressive analgesia. This is particularly useful in critically ill patients who have prolonged stays in the intensive care unit.

Comparison of the analgesic effectiveness of intraveneous or intramuscular opioids, intercostal blocks, epidural morphine, and epidural local anesthetics has been performed.[12, 70, 80] Patients were the most alert

Table 2. INTRASPINAL OPIOIDS FOR POSTTHORACOTOMY PAIN

Drug	Single Dose*	Infusion†	Onset (min)	Duration‡ (h)
Epidural				
Morphine	1–6 mg	0.1–1.0 mg/h	30	6–24
Meperidine	20–150 mg	2–20 mg/h	5	6–8
Fentanyl	25–150 μg	25–100 μg/h	5	3–6
Sufentanil	10–60 μg	10–50 μg/h	5	2–4
Subarachnoid				
Morphine	0.1–0.3 mg		15	8–24
Fentanyl	5–25 μg		5	3–6

*Doses must be carefully adjusted for patient age and catheter position. (See Table 3 for suggested epidural morphine doses.)

†When using epidural infusion, for accuracy and convenience of administration, adjust concentration to allow infused volume to be approximately 10 mL/h. For infusion with bupivacaine, use 0.0625% bupivacaine solution.

‡Duration of analgesia is variable. It tends to increase with dose and patient age.

Table 3. STARTING DOSES FOR EPIDURAL MORPHINE FOR THORACIC ANALGESIA

Patient Age (years)	Catheter Tip at T4–T11 Level (mg)	Catheter Tip at T12–L4 Level (mg)
15–44	4	6
45–65	3	5
66–75	2	4
76+	1	2

Careful consideration must be given to the presence of other concurrent disease and to the response seen with these suggested initial doses.

From Ready LB, Oden R, Chadwick HS, et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988; with permission.

and the most mobile with segmental epidural block with local anesthetic, but the potential for hypotension required close monitoring, and occasionally, vasopressors were also required.[12] Epidural opioid use allowed easier ambulation and also did not impair bowel or bladder function. There also is evidence that epidural morphine may provide not only better analgesia, but also better preservation of pulmonary function in postthoracotomy patients, compared with routine parenteral morphine.[80]

Rostral spread may cause side effects peculiar to epidural opioids, which include nausea, pruritus, and urinary retention as well as the phenomenon of so-called late respiratory depression. The use of lower doses is recommended with catheter placement in the thoracic region to limit rostral spread and therefore to limit side effects. The side effects of nausea, pruritus, and urinary retention can be treated with medication specific for the symptom (such as metoclopramide or prochlorperazine for nausea or diphenhydramine for pruritus) or can be treated with parenteral opioid antagonists, such as naloxone.[87] Systemic use of a mixed agonist-antagonist drug such as nalbuphine also has been shown to be effective in some cases to reverse side effects without reversing analgesia.[37]

Respiratory depression is the most potentially serious side effect of epidural opioids, but also can occur with parenteral opioids as routinely prescribed.[13] Frequent assessment of patient condition remains the most important factor in averting potential problems, regardless of the method of administration of analgesic medication. The incidence of clinically significant, treatable respiratory depression associated with epidural morphine is very small—0.9% in one review,[87] and 0.6% in another.[74] There appear to be two peak times of onset of respiratory depression, one within 1 to 2 hours of epidural morphine administration and another about 6 to 12 hours later. The early peak appears to correspond to systemic absorption of the opioid from the epidural space, and the later peak to rostral spread of the opioid. Most reports describe the gradual onset of respiratory depression, corresponding to rostral migration. Most patients have become sedated before developing respiratory insufficiency. With the gradual accumulation of experience, it has become clear that the use of epidural or intrathecal opioids requires observation of the patient for sedation, rather than for a decrease in respiratory rate, as the earliest sign of impending respiratory depression.[74]

Some institutions have established guidelines regarding whether respiratory monitoring should be instituted, which are described in Table 4.[74] Fear of respiratory depression has influenced some institutions not to allow use of intraspinal opioids anywhere except in an intensive care unit. However, it has become clear that intraspinal opioids can be safely used in ward settings if appropriate guidelines for selection of patients, dosing, and monitoring are used,[60, 73] so the occupation of an expensive and sometimes scarce intensive care unit bed by a patient solely for pain management is unnecessary. The use of a planned dosage scale based on catheter location, surgical site, and the age of the patient may prevent respiratory depression. It is especially important that no additional systemic opioids be given without discussion with a pain management specialist familiar with the use of epidural opiates. Summation of the gradually increasing central effect with the systemic effect of additional opioids may cause severe respiratory depression. Other medications, such as sedatives and tranquilizers (like the benzodiazepines), also may interact with epidural opioids in this fashion.

The treatment of clinically important respiratory depression should be with titrated doses of a narcotic antagonist. Divided doses of naloxone, 0.1 to 0.2 mg, can be given intravenously. Alternatively, 0.4 to 0.8 mg of naloxone can be given intramuscularly. An ampule of naloxone should be kept at the patient's bedside at all times.

With regard to prevention of respiratory depression, the use of a continuous intravenous infusion of naloxone has been recommended.[68, 72] An infusion of up to 5 μg/kg/h of naloxone can be used to prevent the occurrence of signs of respiratory depression (hypercar-

Table 4. CRITERIA FOR DETERMINING WHEN TO USE A RESPIRATORY MONITOR*

A respiratory monitor is not required
  A. When all the following criteria are met
    1. Age <50
    2. ASA physical status I or II
    3. Surgical site: all except thorax or upper abdomen
    4. Duration of surgery <4 h
    5. Anesthetic: little or no narcotics or other long-acting CNS depressants used before or during surgery
    6. Epidural morphine dose of 6 mg or less
       Subarachnoid morphine dose of 0.5 mg or less

or

  B. Postoperative care location provides continuous nursing surveillance

*These are only guidelines. A respiratory monitor may be ordered for any patient at the discretion of the operating room anesthesiologist, the acute pain service, or the unit charge nurse.

From Ready LB, Oden R, Chadwick HS, et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988; with permission.

bia, decrease in respiratory rate, decrease in minute volume), without necessarily decreasing the analgesic effect of the epidural opioid. At rates of infusion over 5 μg/kg/h, however, at least partial reversal of analgesia is common. A similar use of a continuous intravenous infusion of nalbuphine has been described.[3]

Epidural Techniques: Continuous Opioid Infusions

A continuous epidural infusion of 0.1 mg/h of morphine has been shown to improve pain relief and markedly decrease the length of stay in the intensive care unit in a group of patients with blunt chest trauma.[95] Sufentanil has also been infused at a rate of 0.1 μg/kg/h by high thoracic epidural, with good analgesic effect after thoracotomy.[86]

However, there is some question as to whether the main site of action of opioid given by continuous infusion is indeed intraspinal at all. In one study, the circulating levels of fentanyl were the same and pain ratings also were the same whether fentanyl was infused into the epidural space or intravenously.[53] A slow continuous epidural infusion may indeed be administering the opioid into just another parenteral location. However, there may be a combined effect, in that both intraspinal receptors close to the site of injection and other central opioid receptors may be involved in the production of analgesia. With other agents that are less lipid soluble, such as morphine, less systemic absorption may take place, making the intraspinal action more likely to be important.

Epidural Techniques: Combined Local Anesthetic-Opioid Infusions

Combining both types of medication at low doses may give the benefits of each without the severity of side effects seen with each individual drug used its to full effect. The combination of local anesthetic and opioid for epidural infusion may also be synergistic.[1] Continuous infusions of bupivacaine mixed with either morphine, fentanyl, or sufentanil have shown good analgesic results.[28, 36, 39]

Subarachnoid and Epidural Techniques: Other Agents

There are a variety of spinal cord receptors, other than opiate receptors, that can produce analgesia when they are activated.[83, 101] Clonidine (a synthetic α_2-agonist) has been studied in this regard.[8, 29] Clonidine appears to have an analgesic effect of its own, as well a potentiating effect on the intensity of epidural morphine analgesia.[65] However, clonidine also potentiates respiratory depression from epidural morphine,[65] and its epidural administration may be associated with hypotension and bradycardia.[24] At the present time, its use as an analgesic is still investigational.

SPECIFIC ANALGESIC TECHNIQUES: SYSTEMIC APPROACH

Medications Used for Sedation

Benzodiazepines, barbiturates, phenothiazines, and butyrophenones all have been given in conjunction with opioids.[56] They should be used for anxiolysis, sedation, and production of amnesia, and not for analgesia, because they have no analgesic properties. When used for anxiolysis, they also may depress consciousness and ventilation so that endotracheal intubation and mechanical ventilation are necessary. Their main use may well be for patients who will need prolonged ventilatory assistance, and in whom sedation will be helpful during the first 24 to 48 hours postoperatively. They also can be used for anxiolysis during painful bedside procedures.[46] Opioids alone should not be used for sedation.

Systemic Opioid Analgesia

The traditional approach to opioid administration is the deposition of a bolus of drug into a tissue (as an intramuscular or subcutaneous injection). The medication is then absorbed and redistributed according to many variables, which include the blood flow to the tissue in which the depot has been placed. This type of administration is not recommended in the intensive care unit, because perfusion of the muscle and subcutaneous tissue can be quite variable in a critically ill patient, so absorption can be erratic or delayed. The intravenous use of an opioid is therefore preferable to an intramuscular or subcutaneous injection.

Continuous intravenous infusion of opioid is a relatively simple technique and may be preferable to intermittent intravenous bolus dosing. Opioids used systemically must be frontloaded to achieve the minimum effective analgesic concentration in a reasonable length of time. The continuous administration of opioid without frontloading will not result in achievement of the minimum effective analgesic concentration for at least three elimination half-lives.[85] Table 5 provides some simple guidelines for frontloading opioid drugs.[22] After frontloading, a therapeutic blood level of opioid can be maintained by continuous infusion. The rate of infusion can be determined by using a fairly simple calculation, as follows[23]: (1) most opioid drugs have an elimination half-time of about 3 hours; and (2) the dose required every 3 hours to maintain the level of analgesia achieved during frontloading will be one half the dose required to produce analgesia during frontloading. For example, a patient requires 12 mg of intravenous morphine sulfate to obtain analgesia following a hysterectomy. A continuous infusion is to be used: 12 mg/2 = 6 mg eliminated every 3 hours, or 6 mg/3 h = 2 mg/h required. This approximation tends to underestimate the hourly requirement because the elimination half-life is actually less than 3 hours.

Table 5. GUIDELINES FOR FRONTLOADING INTRAVENOUS ANALGESICS

Drug	Total Frontload Dose (mg/kg)	Increments	Cautions
Morphine	0.08–0.12	0.03 mg/kg every 10 minutes	Histamine effects; nausea; biliary colic; reduce dose for elderly
Meperidine	1.0–1.5	0.30 mg/kg every 10 minutes	Reduce dose or change drug for impaired renal function
Codeine	0.5–1.0	One third of total every 15 minutes	Nausea
Methadone	0.08–0.12	0.03 mg/kg every 15 minutes	Do not administer maintenance dose after analgesia achieved; accumulation; sedation
Levorphanol	0.02	50–75 μg/kg every 15 minutes	Similar to methadone
Hydromorphone	0.02	25–50 μg/kg every 10 minutes	Similar to morphine
Pentazocine	0.5–1.0	One half of total every 15 minutes	Psychomimetic effects; may cause withdrawal in narcotic-dependent patients
Nalbuphine	0.08–0.15	0.03 mg/kg every 10 minutes	Less psychomimetic effect than pentazocine; sedation
Butorphanol	0.02–0.04	0.01 mg/kg every 10 minutes	Sedation; psychomimetic effects like nalbuphine
Buprenorphine	Up to 0.2	One quarter of total every 10 minutes	Long-acting like methadone and levorphanol; may precipitate withdrawal in narcotic-dependent patients; safe to give subcutaneous maintenance after analgesia—different from methadone

If breakthrough pain occurs, a new frontload of opioid must be titrated to effect before a new infusion rate is established. Just increasing the infusion rate would leave the patient with nontherapeutic levels for at least three drug half-lives.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is a technique for the administration of small doses of opioid intravenously on a demand basis. Many of the same principles apply as were used in determining intravenous infusion rates. However, requirements for opioids are highest at the beginning of therapy, and even frontloading does not cover all eventualities in this regard. When establishing an upper limit for PCA it is best to take into account as much as a fivefold increase in need during the early postoperative period.[56, 99] Therefore, if one predicts that 2 mg/h should be infused to maintain the minimum effective analgesic concentration for morphine in a particular patient, the 1-hour limit should be set at 10 mg/h. Maintenance (demand) doses should generally not exceed 0.02 mg/kg of morphine (or its equivalent) or 1.5 mg of morphine per dose in most adult patients. Lockout intervals of 5 to 10 minutes are the usual and are used to take account of the time required for a new concentration to be established at the active site before another dose can be given. Breakthrough pain needs to be dealt with as with a continuous infusion, in that an additional frontload will be necessary before a new prescription is started.

Overdose is a low-risk problem with PCA because patients tend to titrate themselves into the therapeutic range and to keep themselves out of the toxic range. Most patients choose not to eliminate pain entirely, but instead to maintain a satisfactory level of analgesia that is individually determined.[4, 44, 89, 90] If the maintenance (demand) dose is overestimated, the patient will become sleepy with each dose and not request additional medication. The serum opioid level will drop as he or she sleeps. Overdose is a more significant risk if a continuous background infusion (basal infusion) is added to PCA. Some machines do not allow such background infusion, but if one is used in an effort to provide longer pain-free periods, no more than half of the predicted hourly requirement should be supplied in this way. Because patients do not control the background infusion, accumulation is possible if the continuous background infusion is set too high.

Lack of adequate analgesia with PCA can result from an inadequate demand dose, failure of the patient to understand the technique, equipment malfunction, or programming errors. Overdose can also occur because of equipment malfunction or programming error[55] or because of administration of drug by someone other than the patient. This can occur often in pediatric patients for whom PCA becomes "parent-controlled" and has been reported once as "spouse-controlled" analgesia.[98] The very nature of PCA requires that patients be awake and cooperative and able to dose themselves on demand. The unconscious, drowsy, or uncooperative patient is not suitable for this technique. It is still unknown whether patients with a history of drug abuse can use PCA effectively.

INFLUENCE OF PAIN CONTROL ON COMPLICATIONS, OUTCOME, AND LENGTH OF STAY

Pulmonary Function and Pulmonary Complications

The prevention of postoperative pulmonary complications (including atelectasis, lung infections, and arterial hypoxemia) is one of the major goals of providing adequate postoperative analgesia. A reduction in functional residual capacity is the most important mechanical abnormality linked to pulmonary complications.[18] This leads to atelectasis when the functional residual capacity falls below closing volume (the lung volume at which small airway closure occurs), which causes arterial hypoxemia. Stasis of secretions also occurs, which leads to a greater potential for pulmonary infections.[6]

Changing the position of the patient from supine to sitting can raise functional residual capacity above the closing volume. Oxygenation then improves.[19] The analgesic techniques described in this article can allow patients greater mobility. This allows the sitting position to be attained earlier, and therefore pulmonary complications from airway closure and atelectasis can be avoided. This has been demonstrated in morbidly obese patients undergoing gastroplasty.[69] Fewer pulmonary complications resulted with epidural narcotic analgesia, compared with traditional intramuscular opioid analgesia, because epidural analgesia allowed earlier patient mobility.

Splinting due to incisional pain definitely decreases function residual capacity, and relief of incisional pain partially restores pulmonary function. Intercostal nerve blocks have been shown to limit the decrease in forced vital capacity and forced expiratory volume in 1 second seen after thoracotomy.[49] This effect has been seen to last for the entire first week after thoracotomy.[92] The use of interpleural bupivacaine analgesia has also been shown to limit decreases in forced vital capacity and forced expiratory volume in 1 second after cholecystectomy.[96] The use of epidural local anesthetics has been shown to improve forced vital capacity relative to control patients after upper abdominal surgery.[82, 97] Analgesia with epidural morphine gives a significantly smaller decrease in forced vital capacity and forced expiratory volume in 1 second than is seen in postthoracotomy patients receiving intravenous morphine for analgesia.[80] PCA has been found to produce higher forced vital capacities in patients after gastric bypass surgery, as compared with traditional intramuscular as-needed narcotic regimens.[5]

There is a strong case to be made that aggressive pain management techniques can benefit overall outcome, especially in patients with severe chest trauma. One study prospectively evaluated 28 patients with multiple rib fractures and compared continuous thoracic epidural morphine analgesia with standard morphine parenteral analgesia.[95] In the epidural morphine group there was a significant decrease in ventilator-dependent time, intensive care unit stay, hospital stay, and a lower incidence of tracheostomy when compared with the control group.

Comparisons have been made among the various central regional analgesic techniques and intramuscular morphine, PCA morphine, and continuous infusion morphine.[14, 20] The use of other aggressive analgesic techniques appears to provide almost the same prevention of decrease in forced vital capacity, forced expiratory volume in 1 second, and functional residual capacity as do epidural techniques. Therefore, if epidural techniques are contraindicated or technically impossible, the other techniques described in this article, if properly applied, may well have the same beneficial effect on postoperative pulmonary function.

Hemodynamic Stability

Painful stimuli evoke a generalized sympathetic response.[62] Use of analgesic techniques other than major regional anesthesia will not prevent the endocrine and metabolic stress response to surgery.[50] However, there is good evidence that intraoperative use of epidural opioids can blunt the sympathetic response following major surgery and therefore improve hemodynamic stability. One recent study examined the effect of epidural morphine on the incidence of postoperative hypertension in patients undergoing operations on the abdominal aorta.[9] Once the patients regained normothermia, there was a lower incidence of hypertension requiring treatment in the epidural morphine group (33%) than in the control group (75%).

Length of Hospital Stay

Patients who received only intercostal blocks for analgesia after cholecystectomy were found to ambulate more quickly and were discharged from the hospital sooner than a control group that received intramuscular meperidine for analgesia.[10] The use of PCA in postthoracotomy patients was found to shorten the length of hospitalization by 22% to 25% when compared with controls who were treated with conventionally administered parenteral analgesics.[27, 78]

SUMMARY

An organized treatment plan for providing analgesia in intensive care settings can make a significant difference in patient comfort, as well as in patient outcome. Advanced analgesic techniques are available for use at each level of the pain pathway. These include agents and methods that act at the periphery, such as nonsteroidal anti-inflammatory drugs and local anesthetics for infiltration or major nerve block or for interpleural block. Techniques that act at the spinal cord level include transcutaneous electrical nerve stimulation, subarachnoid opioids, and epidural opioids and local anesthetics. Finally, a systemic approach can be followed, using opioids parenterally by intravenous bolus, intravenous infusion, or PCA.

Anesthesiologists specially trained in advanced pain management are in a unique position to influence the clinical course of critically ill patients. Their knowledge of pharmacokinetics, their experience with the clinical pharmacology of analgesics, and their knowledge of block procedures prepare them, particularly, for aggressive treatment of pain in the intensive care setting.

References

1. Akerman B, Arwestrom E, Post C: Local anesthetics potentiate spinal morphine antinociception. Anesth Analg 67:943, 1988
2. Bates MS: Ethnicity and pain, a biocultural model. Soc Sci Med 24:47, 1987
3. Baxter AD, Samson B, Penning J, et al: Prevention of epidural morphine induced

respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients. Can J Anaesth 36:503, 1989

4. Bennett RL, Batenhorst RL, Graves DA: Morphine titration in postoperative laparotomy patients using patient-controlled analgesia. Curr Ther Res 32:45, 1982
5. Bennett R, Batenhorst RL, Foster TS, et al: Postoperative pulmonary function with patient-controlled analgesia. Anesth Analg 61:171, 1982
6. Bishop MJ, Cheney FW: Respiratory complications of anesthesia and surgery. Semin Anesth 2:91, 1983
7. Blomberg S, Emanuelsson H, Ricksten SE: Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 69:558, 1989
8. Bloor BC: Clonidine and other alpha-2 adrenergic agonists: An important new drug class for the perioperative period. Semin Anesth 3:170, 1988
9. Breslow MJ, Jordan DA, Christopherson R, et al: Epidural morphine decreases postoperative hypertension by attenuating sympathetic nervous system hyperactivity. JAMA 261:3577, 1989
10. Bridenbaugh PO: Anesthesia and influence on hospitalization time. Reg Anesth 7:S151, 1982
11. Brodsky JB, Kretzschmar KM, Mark JBD: Caudal epidural morphine for post-thoracotomy pain. Anesth Analg 67:409, 1988
12. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. Anesth Analg 59:473, 1980
13. Brose WG, Cohen SE: Oxyhemoglobin saturation following Caesarian section in patients receiving epidural morphine, PCA, or IM meperidine analgesia. Anesthesiology 70:948, 1989
14. Cheng EY, Wang-Cheng RW: Postoperative analgesia and respiratory function. Anesthesiology 71:A663, 1989
15. Conacher ID, Kokri M: Postoperative paravertebral blocks for thoracic surgery. Br J Anaesth 59:155, 1987
16. Conacher ID, Paes ML, Jacobson L, et al: Epidural analgesia following thoracic surgery. Anaesthesia 78:546, 1983
17. Covino BG: Interpleural regional analgesia. Anesth Analg 67:427, 1988
18. Craig DB: Postoperative recovery of pulmonary function. Anesth Analg 60:46, 1981
19. Craig DB, Wahba WM, Don HF, et al: "Closing volume" and its relationship to gas exchange in seated and supine position. J Appl Physiol 31:717, 1971
20. Cuschieri RJ, Morran CG, Howie JC, et al: Postoperative pain and pulmonary complications: Comparison of three analgesic regimens. Br J Surg 72:495, 1985
21. Eason NJ, Wyatt R: Paravertebral thoracic block—A reappraisal. Anaesthesia 34:638, 1979
22. Edwards WT: Optimizing opioid treatment of postoperative pain. J Pain Symptom Management 5(suppl):S24, 1990
23. Edwards WT, Breed RJ: The treatment of acute postoperative pain in the post-anesthesia care unit. Anesthesiol Clin North Am 8:235, 1990
24. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. Anesthesiology 71:640, 1989
25. Faust RG, Nauss LA: Post-thoracotomy intercostal block: Comparison of its effects on pulmonary function with those with intramuscular meperidine. Anesth Analg 55:542, 1976
26. Ferreira SH: Prostaglandin hyperalgesia and the control of inflammatory pain. *In* Bonta IL, Bray MA, Parham MJ (eds): Handbook of Inflammation: The Pharmacology of Inflammation, vol 5. New York, Elsevier, 1985, p 107
27. Finley RJ, Kerri-Szanto M, Boyd D: New analgesic agents and techniques shorten postoperative hospital stay. Pain Suppl 2:S397, 1984
28. Fischer RL, Lubenow TR, Liceaga A, et al: Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesth Analg 67:559, 1988
29. Franz DN, Wong KC: The potential use of clonidine in anesthesia. Literature Scan: Anesthesiology 3:2, 1989
30. Fromme GA, Steidl LJ, Danielson DR: Comparison of lumbar and thoracic epidural morphine for relief of post-thoracotomy pain. Anesth Analg 64:454, 1985

31. Galway JE, Caves PK, Dundee JW: Effect of intercostal nerve blockade during operation on lung function and the relief of pain following thoracotomy. Br J Anaesth 47:730, 1975
32. Gaumann DM, Lennon RL, Wedel DJ: Continuous axillary block for postoperative pain management. Reg Anesth 13:77, 1988
33. Gibbons J, James O, Quail A: Relief of pain in chest injury. Br J Anaesth 45:1136, 1973
34. Gillies GW, Kenny GN, Bullingham BE: The morphine-sparing effect of ketorolac tromethamine. Anaesthesia 42:727, 1987
35. Griffiths DPG, Diamond AW, Cameron JD: Postoperative extradural analgesia following thoracic surgery: A feasibility study. Br J Anaesth 47:48, 1975
36. Hasenbos M, Eckhaus MN, Slappendel R, et al: Continuous high thoracic epidural administration of bupivacaine with sufentanil or nicomorphine for postoperative pain relief after thoracic surgery. Reg Anesth 14:212, 1989
37. Henderson SK, Cohen C: Nalbuphine augmentation of analgesia and reversal of side effects following epidural hydromorphone. Anesthesiology 65:216, 1986
38. Hewitt PB: Subjective follow-up of patients from a surgical intensive therapy ward. Br Med J [Clin Res] 4:669, 1970
39. Hjortso NC, Lund C, Mogensen T, et al: Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. Anesth Analg 65:1033, 1986
40. Hord AH, Roberson JR, Thompson WF, et al: Evaluation of continuous femoral nerve analgesia after primary total knee arthroplasty. Anesth Analg 70:S164, 1990
41. Huskisson EC: Visual analog scales. *In* Melzack R (ed): Pain Measurement and Assessment. New York, Raven Press, 1983, p 33
42. Hymes AC, Yonehiro EG, Raab DE, et al: Electrical surface stimulation for treatment and prevention of ileus and atelectasis. Surg Forum 25:222, 1974
43. James EC, Kolberg HL, Iwen GW, et al: Epidural analgesia for post-thoracotomy patients. J Thorac Cardiovasc Surg 82:898, 1981
44. Johnson LR, Magnani B, Chan V, et al: Modifiers of patient-controlled analgesia efficacy. 1. Locus of control. Pain 39:17, 1989
45. Jones J, Hoggart B, Withey J, et al: What the patients say: A study of reactions to an intensive care unit. Intensive Care Med 5:89, 1979
46. Joshi-Ryzewicz W, Landow L: Anesthesia for bedside procedures. *In* Rippe JM, Irwin RS, Alpert JS, et al (eds): Intensive Care Medicine, ed 2. Boston, Little, Brown, 1991, p 188
47. Kambam JR, Hammond J, Parris WCV, et al: Intrapleural analgesia for postthoracotomy pain and blood levels following bupivacaine intrapleural injection. Can J Anaesth 36:106, 1989
48. Kambam JR, Handte RE, Flanagan J, et al: Intrapleural anesthesia for post thoracotomy pain relief. Anesth Analg 66:S90, 1987
49. Kaplan JA, Miller ED, Gallagher EG: Postoperative analgesia for thoracotomy patients. Anesth Analg 54:773, 1975
50. Kehlet H: Modification of responses to surgery by neural blockade: Clinical implications. *In* Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Pain Management, ed 2. Philadelphia, JB Lippincott, 1988, p 145
51. Kolker A, Patel U, Shah N, et al: Impact of indocin on postoperative opioid requirement following thoracotomy. Anesthesiology 71:A670, 1989
52. Lander J: Clinical judgments in pain management. Pain 42:15, 1990
53. Loper KA, Ready LB, Downey M, et al: Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 70:72, 1990
54. Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 78:173, 1973
55. Mather LE, Owen H: The pharmacology of patient-administered opioids. *In* Ferrante FM, Ostheimer GW, Covino BG (eds): Patient-Controlled Analgesia. Cambridge, Blackwell Scientific, 1990, p 27
56. Mather LE, Phillips GD: Opioids and adjuvants: Principles of use. *In* Cousins MJ, Phillips GD (eds): Acute Pain Management. New York, Churchill Livingstone, 1986, p 77

57. Melzack R: The short form McGill Pain Questionnaire. Pain 30:191, 1987
58. Merskey H, Albe-Fessard DG, Bonica JJ, et al: Pain terms: A list with definition and notes on usage. Pain 7:249, 1979
59. Moore DC: Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. Br J Anaesth 47:284, 1975
60. Mott JM, Eisele JH: A survey of monitoring practices following spinal opiate administration. Anesth Analg 65:S105, 1986
61. Nielsen CH: Bleeding after intercostal nerve block in a patient anticoagulated with heparin. Anesthesiology 71:162, 1989
62. O'Gara PT: The hemodynamic consequences of pain and its management. J Intensive Care Med 3:3, 1988
63. O'Kelly E, Garry B: Continuous pain relief for multiple fractured ribs. Br J Anaesth 53:989, 1981
64. Ottoson D, Lundeberg T: Pain Treatment by Transcutaneous Electrical Nerve Stimulation (TENS), A Practical Manual. New York, Springer-Verlag, 1988
65. Petit J, Oskenheindler G, Colas G, et al: Comparison of the effects of morphine, clonidine and a combination of morphine and clonidine administered epidurally for postoperative analgesia. Anesthesiology 71:A647, 1989
66. Purcell-Jones G, Pither CE, Justins DM: Paravertebral somatic nerve block: A clinical, radiographic, and computed tomographic study in chronic pain patients. Anesth Analg 68:32, 1989
67. Raj P: Intrapleural anesthesia—Applications and contraindications. Anesthesiol Alert 1:1, 1988
68. Rawal N, Schott U, Dahlstrom B, et al: Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 64:194, 1986
69. Rawal N, Sjostrand U, Christoffersson E, et al: Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: Influence on postoperative ambulation and pulmonary function. Anesth Analg 63:583, 1984
70. Rawal R, Sjostrand UH, Dahlstrom B, et al: Epidural morphine for postoperative pain relief: A comparative study with intramuscular narcotic and intercostal nerve block. Anesth Analg 61:93, 1982
71. Rawal N, Tandon B: Epidural and intrathecal morphine in intensive care units. Intensive Care Med 11:129, 1985
72. Rawal N, Wattwil M: Respiratory depression after epidural morphine—An experimental and clinical study. Anesth Analg 63:8, 1984
73. Ready LB, Edwards WT: Postoperative care following intrathecal or epidural opioids II. Anesthesiology 72:213, 1990
74. Ready LB, Oden R, Chadwick HS, et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988
75. Reiestad F, McIlvaine WB, Kvalheim L, et al: Interpleural analgesia in treatment of upper extremity reflex sympathetic dystrophy. Anesth Analg 69:671, 1989
76. Reiestad F, Stromskag KE: Interpleural catheter in the management of postoperative pain, a preliminary report. Reg Anesth 11:89, 1986
77. Rocco A, Reiestad F, Gudman J, et al: Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures, preliminary report. Reg Anesth 12:10, 1987
78. Ross EL, Perumbetti P: PCA: Is it cost effective when used for postoperative pain management? Anesthesiology 69:A710, 1988
79. Seltzer JL, Larijani GE, Goldberg ME, et al: Intrapleural bupivacaine—A kinetic and dynamic evaluation. Anesthesiology 67:798, 1987
80. Shulman M, Sandler AN, Bradley JW, et al: Postthoracotomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 61:569, 1984
81. Shuman RL, Peters RM: Epidural anesthesia following thoracotomy in patients with chronic obstructive airway disease. J Thorac Cardiovasc Surg 71:82, 1976
82. Simpson BR, Parkhouse J, Marshall R, et al: Extradural analgesia and the prevention of postoperative respiratory complications. Br J Anaesth 33:628, 1961
83. Sosnowski M, Yaksh TL: Role of spinal adenosine receptors in modulating the hyperesthesia produced by spinal glycine receptor antagonism. Anesth Analg 69:587, 1989

84. Squier RC, Morrow JS, Roman R: Hanging-drop for intrapleural analgesia. Anesthesiology 70:882, 1989
85. Stanski DR, Watkins DW: Drug Disposition in Anesthesia. Orlando, Grune & Stratton, 1982, p 1
86. Stanton-Hicks MDA, Gielen M, Hasenbos M, et al: High thoracic epidural with sufentanil for post-thoracotomy pain. Reg Anesth 13:62, 1988
87. Stenseth R, Sellevold O, Breivil H: Epidural morphine for postoperative pain: Experience with 1085 patients. Acta Anaesthesiol Scand 29:148, 1985
88. Stoelting RK: Intrathecal morphine—An underused combination for postoperative pain management. Anesth Analg 68:707, 1989
89. Tamsen A: Patient characteristics influencing pain relief. *In* Harmer M, Rosen M, Papper EM (eds): Patient-Controlled Analgesia. Oxford, England, Blackwell Scientific, 1985, p 30
90. Thompson CC, Bailey MK, Conroy JM, et al: Patient-controlled analgesia—Advances in the last five years. Anesthesiol Rev 3:14, 1989
91. Toft P, Jorgensen A: Continuous thoracic epidural analgesia for the control of pain in myocardial infarction. Intensive Care Med 13:388, 1987
92. Toledo-Pereyra LH, DeMeester TR: Prospective randomized evaluation of intrathoracic intercostal nerve block with bupivacaine on postoperative ventilatory function. Ann Thorac Surg 27:203, 1979
93. Tverskoy M, Cozacov C, Ayache M, et al: Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 70:29, 1990
94. Tyler E, Caldwell C, Ghia JN: Transcutaneous electrical nerve stimulation: An alternative approach to the management of postoperative pain. Anesth Analg 61:449, 1982
95. Ullman D, Fortune SB, Greenhouse BB, et al: The treatment of patients with multiple rib fractures using continuous thoracic epidural narcotic infusion. Reg Anesth 14:43, 1989
96. VadeBoncouer TR, Riegler FX, Gautt RS, et al: A randomized, double blind comparison of the effects of intrapleural bupivacaine and saline on morphine requirements and pulmonary function after cholecystectomy. Anesthesiology 71:339, 1989
97. Wahba WM, Craig DB, Don HF: Postoperative epidural analgesia: Effect on lung volumes. Can Anaesth Soc J 22:519, 1975
98. Wakerlin G, Larson CP Jr: Spouse-controlled analgesia. Anesth Analg 70:119, 1990
99. White PF: Patient-controlled analgesia: A new approach to management of postoperative pain. Semin Anesth 4:255, 1985
100. Woolf CJ: Recent advances in the pathophysiology of acute pain. Br J Anaesth 63:139, 1989
101. Yaksh TL, Aimone L: The central pharmacology of pain transmission. *In* Wall PD, Melzack R (eds): Textbook of Pain. Edinburgh, Churchill Livingstone, 1989, p 181
102. Yeager MP, Glass DD, Neff RK, et al: Epidural anesthesia and analgesia in high risk surgical patients. Anesthesiology 66:729, 1987

Address reprint requests to

Donald S. Stevens, MD
Department of Anesthesiology
University of Massachusetts Medical Center
55 Lake Avenue North
Worcester, MA 01655

COMPLICATIONS OF ACUTE PAIN MANAGEMENT

Richard C. Etches, MD, FRCP(C)

Historically, the management of acute pain in hospitalized patients has been inadequate, with greater than 50% of patients experiencing distressing pain.[25] Since 1980, however, several developments, especially patient-controlled analgesia (PCA), spinal opioid analgesia, and the concept of the anesthesiology-based acute pain management service, allow the provision of analgesia for many patients that is clearly superior to that provided by conventional intramuscular (IM) opioids. There is also a growing body of evidence that improved analgesia may be associated with less morbidity and mortality and with lower costs of hospitalization.[51, 52, 56, 59, 70, 74]

The traditional management of postoperative pain, IM opioid administration, does have the apparent virtue of simplicity. In contrast, the safe use of techniques such as PCA and spinal opioid analgesia is dependent on specialized training of nursing staff, the availability and technical expertise of the interested anesthesiologist, and the reliability of complex and expensive electronic infusion pumps.

This article discusses the complications, including those considered side effects and those due to misadventure, of opioid-based acute pain management. Side effects include problems that develop despite appropriate technique and drug administration. Misadventure includes problems that develop because of errors in technique or drug administration and problems associated with equipment failure.

From the Department of Anesthesia, University of Alberta Hospitals, Edmonton, Alberta, Canada

COMPLICATIONS

Side Effects

Opioids still represent the cornerstone of acute pain management in hospitalized patients and may be administered orally, transdermally, IM, intravenously (IV) via PCA, or spinally. Regardless of the route of administration, an adequate dose of drug will produce good analgesia. However, as the dose increases so does the probability of clinically significant side effects. These include nausea, vomiting, pruritus, urinary retention, and CNS depression, especially respiratory depression. Other problems that may be significant but are not well studied include acute psychiatric disturbances, confusion, dizziness, orthostatic hypotension, and constipation.

Nausea and Vomiting

Nausea and vomiting occur frequently following surgery, especially subsequent to procedures performed on the middle or inner ear and gastrointestinal tract, with an reported incidence of 20% to 55%.[49] Important contributory factors, apart from opioid administration, include pain, hypotension, gastric distension, and motion. Women are reported to be two to three times more susceptible to opioid-induced postoperative nausea and vomiting than are men.[8, 49, 53]

The mechanism of opioid-induced nausea and vomiting has been defined: Opioids not only directly stimulate the chemoreceptor trigger zone of the brain stem but also may cause decreased gastric emptying and hypotension, both potent stimuli of the vomiting center. Delayed gastric emptying is due in part to the direct action of opioids at the mu- and delta-receptors, which inhibits the acetylcholine-induced smooth muscle contraction of the gut. However, inhibition of gastric emptying also can be demonstrated by injection of opioids into the CSF at the level of the fourth ventricle or spinal cord.[32] In contrast, pain is also a stimulus for nausea and vomiting, and opioids given for the relief of pain may be antiemetic.[8] All opioids in clinical use may produce nausea and vomiting, and at equianalgesic doses, there is little evidence to favor one over another. However, an individual patient may react adversely to one drug and not another.[33]

The route of administration does not appear to influence the incidence of nausea and vomiting. Three studies that compared epidural morphine, 5 mg, to IM and/or intravenous (IV) PCA morphine in patients following cesarean section found no difference in the incidence of nausea and vomiting between the groups,[16, 20, 30] although in two of the studies there was a trend toward greater nausea and vomiting in the patients who received epidural morphine.[16, 20] It should be noted that many clinicians now administer only 3 to 4 mg of epidural morphine following cesarean section, and this smaller dose may be associated with fewer symptoms. Rapp et al,[53] in a large retrospective review of patients undergoing major gynecologic procedures, found that nausea and vomiting occurred with a similar frequency in patients receiving morphine postoperatively by PCA or epidural catheter; 21% and 28%, respectively. In a comparison of IV and epidural fentanyl infusions following anterior cruciate ligament repair, Loper et al[40] found no difference in the incidence of nausea: 65% overall.

The relationship between the dose of opioid administered and incidence of nausea and vomiting is not consistent. In patients undergoing laparotomy for gynecologic procedures, Owen et al[48] compared postoperative morphine administered via PCA alone or with a background infusion. Pain scores were equivalent, but the group receiving PCA and an infusion received twice as much morphine in the first 24 hours following surgery. Despite the higher morphine demand, this group had lower nausea scores and received less antiemetic medication. In a similar study of PCA morphine with and without a background infusion in patients following cesarean section, Sinatra et al[61] found no difference in morphine requirements between the groups, but patients who received PCA with a background infusion had more nausea requiring treatment. It is difficult to reconcile these apparently contradictory data. Following epidural morphine, Stenseth et al[63] found that 34% of 1085 patients experienced nausea, and this was not related to the total dose administered. However, two studies of the effects of intrathecal morphine, one following cesarean section[1] and the other following transurethral resection of the prostate,[34] demonstrated more frequent nausea and vomiting as the dose increased.

Prevention and treatment of postoperative nausea and vomiting remains a problem. Prophylactic administration of antiemetics perioperatively is unreliable, associated with significant side effects, and is recommended only for selected cases.[49] Transdermal scopolamine has been used prophylactically in patients before the administration of epidural morphine. A decrease in the incidence of nausea and vomiting was apparent,[36, 39] but the frequency of observed side effects, especially dry mouth (67%), drowsiness (18%), and disorientation (1%), limits its widespread application. Scopolamine should not be used in elderly patients because it may cause urinary retention, acute confusion, and toxic psychoses.[8]

Patients who suffer from nausea, vomiting, or pruritus (see following section) following administration of epidural or intrathecal morphine often respond well to small doses of naloxone. However, the prophylactic administration of opioid antagonists is less successful. Naloxone given as a continuous infusion or naltrexone (a long-acting opioid antagonist) given orally may decrease nausea and vomiting, but are associated with a shorter duration of analgesia and higher pain scores following a single dose of epidural or intrathecal morphine.[2, 29] Given the added complexity of a continuous infusion of naloxone and the protracted effect of naltrexone, it is difficult to justify the prophylactic administration of these drugs.

When nausea and vomiting occur, treatment should first be directed to general supportive measures. Hypotension and hypovolemia, if present, should be corrected, and if the patient is in pain, this should be managed with additional analgesics. Consideration then may be given to specific antiemetic therapy. The preference of the author is to prescribe metoclopramide as a first choice; although extrapyramidal side effects and sedation may occur, they are not common. If symptoms persist, antihistamines or phenothiazines may be used. Scopolamine, first parenterally, then transdermally, is often useful in refractory cases. When symptoms are severe and poorly responsive to antiemetic therapy, one should give early consideration to an alternative opioid. For patients who have received epidural or intrathecal opioids, small doses of parenteral naloxone may reverse symptoms if these are due primarily to the effects of the opioid; however, considering the numerous causes of postoperative nausea and vomiting, this approach may be ineffective.

Pruritus

Pruritus is associated with epidural or intrathecal opioid use, with a reported incidence of from 0% to 100%.[57] In fact, it is a common side effect of opioids regardless of the route of administration. The cause of pruritus remains unknown. Pruritus following morphine or meperidine administration has been attributed to histamine release, but this cannot be a complete explanation. Fentanyl and sufentanil, for example, do not release histamine, yet the incidence of pruritus is similar to that for morphine. In addition, antihistamines are often ineffective in treating pruritus caused by spinal opioid administration, whereas naloxone usually provides prompt relief.[19] Pruritus is common following very small doses of intrathecal morphine (0.1–0.25 mg),[1] and patients often present with facial pruritus several hours after drug administration. The extremely small dose implies that the effect is centrally mediated,[3] and the delayed onset of symptoms is consistent with the time required for cephalad spread of the drug within the CSF to the brain stem and fourth ventricle.[22]

For morphine there is considerable evidence that the incidence and severity of pruritus varies depending on the route of administration. Pruritus is most frequently a problem when morphine is administered epidurally or intrathecally, less so with PCA morphine, and least with IM administration[16, 20, 30, 41, 42] (Table 1). For fentanyl the limited evidence suggests that the route of administration is not as important a determinant of pruritus. In patients who received either IV or epidural fentanyl infusions following cesarean section, Ellis et al[21] found no difference in the severity of pruritus when measured using a visual analogue scale; however, more patients in the epidural group requested treatment for pruritus. In a similarly designed study, Loper et al[40] found no difference in the incidence of pruritus requiring treatment when fentanyl was administered IV or epidurally following knee surgery.

The relationship between the dose of an opioid and the incidence of pruritus is not well documented, but two studies have demonstrated a positive correlation following intrathecal[1] or epidural[38] morphine administration. These data support the subjective impression of the

Table 1. PRURITUS FOLLOWING MORPHINE ADMINISTRATION

Reference	Pruritus	Route of Administration IM	PCA	Epidural
Harrison et al[30] (1988)	Present	17	38	73
	Treated	6	11	45
Eisenach et al[20] (1988)	Present	35	60	85
	Treated	5	5	40
Daley et al[16] (1990)	Present	46	N/A	91
	Treated	15	N/A	40
Loper and Ready[42] (1989)	Present	N/A	35	73
	Treated	N/A	17	26
Loper et al[41] (1989)	Present	N/A	N/A	N/A
	Treated	N/A	4	33

All values given as percentage of total.

author and others (GH McMorland, MD, personal communication, 1990) that for patients who receive epidural morphine following cesarean section, the incidence and severity of pruritus are less with 3 mg than with 5 mg of morphine.

Pruritus is a particularly common side effect of epidural morphine administered after cesarean section. Whether this is specific to cesarean section per se or reflects the normal response of young healthy subjects is unknown. An unexpected and puzzling finding is the clear association between epidural morphine administration following cesarean section and the subsequent appearance of herpes labialis (cold sores). Crone et al[13] found that 22% of such patients who were previously seropositive developed herpes labialis 2 to 5 days postoperatively. The cause of herpes labialis in these patients is unknown, but it is possible that facial pruritus may stimulate reactivation of the virus.[27]

Pruritus following administration of IM or IV opioids is usually responsive to antihistamines such as hydroxyzine or diphenhydramine[30]; this supports the role of histamine release and its effects on peripheral nerve endings.[26] In contrast, the pruritus commonly seen following spinal opioid administration is often unresponsive to antihistamines. Small doses of naloxone (e.g., 40 μg IV or 100–200 μg IM) are generally effective in treating the pruritus without reversing the analgesia. If symptoms reappear, a naloxone infusion is occasionally required. Alternatively, oral naltrexone[2] or IV nalbuphine[50] may be helpful. Prophylactic naloxone infusions have been suggested as a method for preventing rather than treating pruritus,[29] but this is generally unnecessary. With the exception of cesarean section patients, pruritus is usually mild and the patients do not request treatment, even when asked. If treatment is required, one or two doses of naloxone is usually sufficient, even after cesarean section. Only a small minority of patients require a naloxone infusion.

Urinary Retention

Retention of urine after anesthesia and surgery is common and is a potential cause of significant postoperative morbidity. Bladder distension and subsequent injury may result in persistent problems with micturition, and catheterization may result in urinary tract infections or, rarely, hematogenous spread of infection to the surgical site.

Opioids, especially spinal opioids, are an important cause of urinary retention in postoperative patients. However, they are not be the only cause. Studies in human volunteers have demonstrated that IV morphine, 10 mg, has little effect on micturition; voiding is not impaired[7]; and urodynamic studies are almost unchanged.[55] Yet up to 40% of patients who receive IM or IV opioids after major surgery suffer from retention.[40, 42, 69, 75] Other contributing factors include pain, sedation, the supine position, and the anticholinergic effects of drugs such as antiemetics.

The reported incidence of urinary retention following spinal opioid administration may be lower than the true incidence; most patient who receive epidural opioids have undergone major surgical procedures and may therefore have a urinary catheter inserted at the time of surgery. Despite this bias, the reported incidence of retention associated with spinal morphine is much higher than that for other parenteral routes.

Bromage et al[7] found that urinary retention developed in 9 of 10 healthy male volunteers who received epidural morphine, 10 mg, and six required naloxone to relieve symptoms. Following orthopedic surgery, the incidence of retention ranges from 48% to 62% when patients receive epidural morphine, compared with 12% to 24% when morphine or meperidine are given IM or IV.[38, 42, 69] In contrast, retention occurred with the same frequency (30%–40%) when patients received fentanyl either IV or epidurally after knee surgery[40]; whether this represents a true difference with fentanyl or is an isolated anomaly is unknown. Reviewing the charts of 1085 adult patients who had undergone thoracotomy, laparotomy, or major orthopedic procedures, Stenseth et al[63] found that the overall incidence of retention was 42% and was unrelated to the surgical site.

It is often suggested that the incidence of postoperative urinary retention is increased in elderly men, but this is not supported by the literature. Walts et al[69] found that age and sex did not correlate with the need for catheterization following hip arthroplasty regardless of analgesic technique (i.e., epidural or IM opioids). However, it is possible that elderly men are more prone to develop refractory bladder outlet obstruction secondary to repeated or traumatic catheterization. Although the data are limited, retention appears to occur with a similar frequency in children who receive epidural morphine, with a reported incidence of 27% to 46%.[68]

The physiology of micturition is complex. Under normal circumstances the bladder will accommodate 400 mL of urine before the voiding phase of the micturition cycle is initiated. Micturition is a voluntary act that is subject to cortical inhibition if desired. If micturition is to proceed, several reflex actions occur. First, the pelvic floor muscles, normally tonically active and responsible for the maintenance of external urethral sphincter tone, relax. The detrusor muscle of the bladder then contracts and the bladder empties. This phase is followed by bladder relaxation and the return of muscle tone to the pelvic floor. The innervation of the bladder, urethra, and pelvic floor is complex. The bladder receives its parasympathetic innervation from the sacral plexus (S2–4) and its sympathetic innervation, mainly β_2, from the hypogastric plexus (T10–L2). The striated (voluntary) muscle of the pelvic floor receives its innervation from the pudendal nerve, but the external urethral sphincter also has a smooth muscle component with parasympathetic and sympathetic innervation, mainly α_1, similar to the bladder.[67]

The neuropharmacologic basis of urinary retention following epidural or intrathecal opioid administration has not been fully elucidated, but recent animal studies clearly demonstrate that the effect occurs at the level of the spinal cord. Durant and Yaksh[18] studied the effects of lumbar intrathecal morphine in unanesthetized rats with chronically implanted suprapubic catheters. Within 15 minutes of morphine administration the detrusor muscle relaxed and no further bladder contractions occurred; the duration of this effect corresponded to the duration of analgesia (as measured by tail flick). In addition, bladder relaxation was accompanied by an increase in urethral sphincter tone. Similar bladder relaxation and loss of micturition reflex following spinally administered morphine has been demonstrated in dogs[17] and humans,[55] and external sphincter tone may also increase in humans.[73] To explain these findings, Durant and Yaksh suggested that intrathecal morphine may inhibit primary parasympathetic afferent activity from the bladder and inhibit both parasympathetic and somatic outflow to the bladder, urethra, and pelvic floor.

In the absence of spinal opioids, several autonomically active drugs have found a place in the management of retention due to poor bladder tone or incomplete outlet obstruction. Bethanechol, a cholinergic agonist, increases bladder tone and is useful in the setting of postoperative and postpartum retention.[64] α-Antagonists, including prazosin and phenoxybenzamine, decrease urethral resistance in patients with benign prostatic hypertrophy.[31] The effectiveness of these drugs in the treatment of opioid-induced retention is uncertain. In human volunteers with retention after epidural morphine, 10 mg, bethanechol facilitated voiding in only two of six subjects; in two subjects bethanechol caused bladder discomfort but did not facilitate voiding and in two the drug had no effect.[7] In a controlled trial phenoxybenzamine was effective in preventing retention in patients who received epidural morphine, 4 mg, after cesarean section. Patients received phenoxybenzamine, 10 mg orally, 24 and 2 hours preoperatively and 8 and 16 hours postoperatively. Ten percent of treated patients required catheterization, compared with 47% of those untreated.[23] In rats, the dopamine agonist apomorphine effectively restored detrusor muscle activity and lowered urethral resistance.[18] In humans the use of apomorphine is clearly unacceptable because of its potent emetic properties, but it is possible that other dopamine agonists may have a role. Bromocriptine, for example, has had limited success in the treatment of some disorders of micturition.[24] Intravenous naloxone is unequivocally effective, but only when given in a dose that also reverses the analgesic effects of opioids.[55]

There is no established pharmacologic approach to the management of urinary retention following spinal opioid administration. α-Antagonist drugs may have a role if the cardiovascular side effects are minimal. The potential role of bromocriptine is unknown. At present, retention is managed by regularly assessing the patient for the presence of bladder discomfort or distension, and catheterizing the bladder if indicated. Our current policy following major hip and knee surgery, regardless of the route of opioid administration, is to perform up to two "in-and-out" catheterizations, then insert an indwelling catheter if necessary.

Respiratory Depression

The subject of postoperative respiratory depression was rarely a source of discussion among anesthesiologists until 1979, when the first reports of profound respiratory depression following intrathecal and epidural opioids began to appear in the literature.[22] Subsequent research has confirmed that some patients who receive spinal opioids will develop severe respiratory depression, and many anesthesiologists have therefore restricted this route of administration to patients who will be continually monitored postoperatively. But the problems associated with spinal opioids must be kept in perspective; in particular, one must remember that opioids in sufficient dose, by any route of administration, will cause potentially life-threatening respiratory depression. Therefore, the safety of one technique over another will always be relative. To illustrate this point, the author has found only two reports of deaths due to opioid-induced respiratory arrest in postoperative patients; one associated with oral sustained-release morphine[5] and another associated with PCA.[37] The author has seen no published reports of deaths due to spinal opioid-induced respiratory arrest.

Postoperative respiratory insufficiency is multifactorial in etiology. Centrally, respiration is depressed by opioids and the residual effects of anesthetic drugs; however, this may be partially offset by the central respiratory stimulant effect of pain. Peripherally, functional residual capacity is decreased, ventilation to perfusion mismatch is increased, and diaphragmatic function is often impaired. These changes are especially severe and persistent after upper abdominal or thoracic surgery. Upper abdominal or thoracic pain, if poorly treated, will further aggravate respiratory insufficiency. Further respiratory problems, especially atelectasis, often develop if the patient is either too sore or too sedated to move about or cough. The goals of analgesic therapy are to provide effective analgesia yet avoid excessive sedation and respiratory depression.

For several reasons it is difficult to determine the relative frequencies of clinically significant respiratory depression when comparing spinal opioid administration with PCA, IM, and other routes. To date, much of the literature has considered respiratory depression as synonymous with hypoventilation and a depression of the CO_2 response curve. This definition is somewhat misleading and limited in scope because it fails to consider the critical problem of an impaired response to hypoxia. From a practical point of view, however, the response to CO_2 may be studied without the ethical constraints that limit the study of the hypoxic response in humans. Many studies have incorrectly defined respiratory depression as a low respiratory rate; except at its extremes, respiratory rate correlates very poorly with $Paco_2$. Also, blinded, prospective studies of homogeneous patient populations are few; instead, data often come from uncontrolled retrospective chart reviews.

There is no doubt that with adequate doses of opioids, regardless of route, we can provide effective analgesia. But when used in a prudent manner, does the incidence of clinically significant respiratory depression differ between routes of administration, techniques, or drugs? For parenteral morphine the incidence of life-threatening respiratory depression has been cited as 0.9%; this datum is from a retrospective review of 860 patients.[45] Catley et al[9] suggest that potentially serious problems occur much more commonly. They found that in the first 16 hours following cholecystectomy or hip arthroplasty 10 of 16 patients receiving IV morphine infusions experienced episodes of pronounced hemoglobin oxygen desaturation (<80%) for periods of up to 120 seconds. In contrast, patients who received epidural bupivacaine for analgesia did not experience any periods of hemoglobin oxygen saturation less than 90%. For PCA, there are no large-scale reviews of the subject, but approximately 1% of our patients who have received PCA have required naloxone for excessive sedation or proven hypoventilation. For epidural and intrathecal morphine, the incidence of serious problems (excluding problems in the recovery room) is similarly low. Rawal et al[54] found an incidence of 0.36% and 0.09% for intrathecal and epidural morphine, respectively. It is noteworthy that the reported incidence of serious problems attributable to spinal morphine has decreased over the last decade. This may be due to the administration of smaller doses and to a greater appreciation of which patients may be at risk. On balance, there is little evidence that route of administration is an important determinant of risk if the dose of drug is appropriate. Conversely, one wonders how many relatively high-risk patients who receive IM morphine as needed on the ward experience potentially dangerous hypoxia.

It has been suggested that the incidence of respiratory depression may be less after the epidural administration of highly lipophilic opioids such as fentanyl or sufentanil. Because of their rapid uptake by the tissues, the cephalad spread of such drugs in the CSF may be less than that of morphine, a hydrophilic drug.[11, 22] However, there are now numerous reports in the literature that document both early and late respiratory depression following the epidural administration of these drugs[4, 6, 57, 58, 62, 72] and in this context they confer no proven advantage.

The dose of opioid, not lipophilicity, appears to be the more important determinant of respiratory depression.

What patient factors may contribute to postoperative respiratory depression? Although this question has not been addressed in the context of parenteral administration, it has been studied with respect to spinal opioids. Not surprisingly, elderly, debilitated patients, patients with preexisting respiratory disease, and those patients who receive large or repeated doses are at increased risk. In addition, patients who undergo thoracic or upper abdominal surgery may be predisposed to respiratory failure. It is reasonable to assume that these risk factors are important, regardless of the route of opioid administration. For spinal opioids, serious respiratory depression may be more common following thoracic epidural opioids, and is definitely associated with the concomitant administration of opioids by other routes.[22]

Misadventure

As pain management has improved over the last decade it has become more complex and more dependent on sophisticated technology. With increasing complexity and technologic dependence comes a greater potential for errors, accidents, and equipment failure.

At least one death[37] and several "near misses"[47, 66, 71] have been attributed to operator errors or equipment failure while using PCA devices. Operator errors included incorrect programming, failure to install a one-way Y connector that allowed the analgesic-containing solution to accumulate in the IV tubing, and inadvertent administration of a large bolus of opioid when changing the syringe on the PCA pump. Equipment failure included apparent pump runaway, pump self-triggering, and a cracked preloaded glass syringe that then permitted simple gravity flow of the opioid solution. These potential problems are summarized in Table 2.

With epidural opioids the major cause of concern has been drug errors, either the administration of an overdose[15] or the administration

Table 2. POTENTIAL PROBLEMS OF PCA LEADING TO OVERDOSE

- Operator errors
  - Wrong drug or concentration
  - Programming errors
  - Improper set-up of syringe and tubing
  - Accidental bolus administration during tubing or syringe change
- Patient errors
  - Poor comprehension
  - Intentional tampering
- Mechanical problems
  - Pump runaway
  - Siphoning

of the wrong drug or diluent.[35, 65] Of particular concern is the possibility that the epidural catheter port or infusion tubing will be mistaken for an IV line. Recent reports describe the placement of indwelling interpleural[12] and femoral sheath[14] catheters for delivery of postoperative analgesics. With this potential proliferation of catheters in otherwise routine postoperative patients, the likelihood of errors must certainly increase. To prevent such accidents, the first line of defence is education of the medical and nursing staff. Additional measures include the elimination of all injection ports and the clear labeling of the epidural catheter, injection port, and infusion line.

PREVENTION OF COMPLICATIONS

The Acute Pain Service

Acute pain management has become more complex, and the anesthesiologist has become a frequent participant in postoperative patient care. As a result, nursing skills and responsibilities have changed, and new lines of communication have been established between the anesthesiologist and the patient, nurse, and surgeon. When serious problems occur, they often indicate deficiencies in administration and organization that have lead to a failure of medical or nursing care. A formally structured acute pain service addresses these problems of administration and organization.

Administrative Responsibilities of the Anesthesiologist

A knowledge of risk factors helps one to identify those patients who may require more specialized postoperative care and monitoring, but even in the absence of risk factors problems will still occur. To provide postoperative analgesia safely and effectively, one must provide for the educational needs of the nurses and physicians, develop appropriate policies and procedures, and clearly define the role of the anesthesiologist in patient care. These responsibilities are time-consuming and often frustrating to the anesthesiologist unaccustomed to administrative work; however, they are the essential foundation on which an acute pain service is built.

Education

Without the active support of the nursing staff, acute pain management will not be optimal. The first step in enlisting this support is to involve the department of nursing in in-service education and policy and procedure development. The educational needs of the nursing staff will vary depending on the pain management techniques used, but some general principles apply. Education should precede clinical application and should include an overview of the relevant anatomy, physiology, pharmacology, and goals of therapy in addition to the complications. There should be clear instruction regarding patient monitoring and potential problems, and their treatment should be objectively defined. The nurses must know who to contact when problems arise.

Physicians also will benefit from additional education. Not all anesthesiologists will be familiar and comfortable with PCA or spinal opioids, and it is valuable to review such subjects at departmental rounds if errors in judgement are to be avoided. Surgical staff should understand the goals and limitations of acute pain management techniques, and there must be a clear understanding between physicians as to who is taking responsibility for pain management. This reduces the possibility that two physicians will be writing conflicting and potentially dangerous orders simultaneously.

Policies and Procedures

Medical and nursing policies must be developed that define the respective roles of nurses and physicians. For example, will nurses administer epidural opioids and if so, how will they be trained? Will such a policy be hospital-wide or only on selected wards? Standards for patient monitoring must be determined: is it appropriate, in a particular hospital, to allow postoperative patients who have received epidural morphine to return to the general surgical ward rather than a step-down unit? Similar questions apply to PCA. The responsibility of the pain management physician versus the surgeon must be clearly defined. It is the author's preference that the acute pain physician writes all orders for analgesics, sedatives, and antiemetics until the patient can manage on routine oral analgesics that are ordered by the surgical staff.

Nursing policy defines what the nurse may do, and nursing procedure describes how it will be done. Nursing procedure dictates how a patient is to be monitored and how complications are to be managed. In the case of the patient who is receiving epidural opioids, nursing procedure describes how top-ups may be administered, what respiratory monitoring is required, the care of the epidural catheter, and the management of respiratory depression. As pain management has become more complex and varied, so have the nurses' duties. Preprinted physicians' order forms that include recommended monitoring, management of complications, and the pager number of the on-call physician and nurse specialist contribute greatly to safe nursing care.

The Role of the Nurse Specialist

More complicated therapy produces more complicated problems, and patients will require attention because of inadequate analgesia, complications, or equipment problems. In addition to the pain management physician, who must always be available, a clinical nurse specialist with a commitment to acute pain management is a valuable asset. The nurse specialist can assist ward nurses with PCA pump operation and answer questions with respect to the care of patients who are receiving epidural opioids. In addition, the nurse specialist is often less threatening to the nursing staff and may therefore be called before errors occur or problems develop.

Opioid-Sparing Strategies

The primary goal of postoperative pain management is to provide good analgesia with minimal side effects. With opioids there is a dose-related increase in the incidence and severity of side effects, especially respiratory depression, and several strategies exist to decrease the amount of opioid required, either as a bolus injection or as a cumulative total.

Most studies of PCA do not demonstrate a lower cumulative dose, but PCA may decrease the problem of periodic sedation seen with repeated IM bolus injections of opioids. However, most studies show little difference in the incidence of side effects when PCA is compared with the IM route. Although evidence is lacking, it is likely that the side effects of epidural morphine will be less if patients receive smaller, more frequent doses. This approach poses considerable practical problems unless the nurse may administer epidural morphine.

Long-acting local anesthetics may decrease or eliminate the need for parenteral opioids postoperatively. Techniques include local infiltration, interpleural catheters, major nerve or plexus blocks, and epidural and caudal analgesia. In obstetrics, fentanyl added to infusions of dilute bupivacaine (0.0625%–0.125%) provides improved analgesia for labor, with a lower cumulative dose of local anesthetic and less motor blockade.[10, 43] Conversely, the addition of low concentrations of local anesthetics to epidural opioid infusions may have a significant opioid-sparing effect; to date, few data are available.

Other drugs with significant analgesic effects may reduce postoperative opioid requirements. Some nonsteroidal anti-inflammatory drugs including indomethacin,[60] diclofenac,[46] and ketorolac[28] administered rectally, IM, or IV have been shown to reduce parenteral morphine requirements by 30% to 60%. Clonidine, an α_2-agonist, may have a morphine-sparing effect when given parenterally or spinally, but sedation and hypotension are frequent problems.[44] Whether the morphine-sparing effect offsets the added cost and potential side effects of these drugs remains to be determined. Even if a marked morphine-sparing effect is demonstrated, we still do not know how that will affect the incidence and severity of side effects.

SUMMARY

Acute pain management is rapidly evolving to become a challenging and gratifying subspecialty of anesthesiology that allows the anesthesiologist to extend his or her skills beyond the confines of the operating room. But our enthusiasm must be tempered by caution. Do the benefits outweigh the costs? There is still only preliminary evidence that improved analgesia has a salutary effect on outcome. However, as pain management becomes more complex, so too does the management and prevention of side effects, errors, and accidents.

Problems common to opioid use by all routes of administration include nausea and vomiting, pruritus, and urinary retention; they are rarely dangerous but often distressing to the patient. Much more serious is the potential problem of respiratory depression. The overall incidence of dangerous respiratory depression is approximately 1%, regardless of route of administration, although patients who receive thoracic epidural opioids may be at increased risk. Other important factors include the general health of the patient, the dose administered, and in the case of spinal opioids, the concomitant administration of parenteral opioids. Errors in drug administration still account for many of the serious problems encountered with PCA and spinal opioid administration. With PCA, common errors include improper set up of the syringe and tubing and errors in programming. Fortunately, serious technical problems with PCA devices are rare. With epidural opioids errors include administration of the wrong dose or the wrong drug.

The first line of defense against serious complications is to provide the necessary education and to develop the necessary policies and procedures that will permit nurses and physicians to safely care for these patients. Strategies directed at reducing or eliminating opioid administration are of secondary importance but are potentially exciting developments.

Over the last four decades anesthesiology has progressed and matured to the point where it is difficult for the careful and prudent anesthesiologist to further improve surgical outcome by changes in the intraoperative management of anesthesia. The acute pain management service takes us beyond the operating room and provides us with a new and exciting opportunity to further improve patient care. The challenge is to ensure that the good we do outweighs the harm.

References

1. Abboud TK, Dror A, Mosaad P, et al: Mini-dose intrathecal morphine for the relief of post-cesarean section pain. Anesth Analg 67:137, 1988
2. Abboud TK, Lee K, Reyes A, et al: Prophylactic oral naltrexone with intrathecal morphine for cesarean section: Effects on adverse reactions and analgesia. Anesth Analg 71:367, 1990
3. Ballantyne JC, Loach AB, Carr DB: Itching after epidural and spinal opiates. Pain 33:149, 1988
4. Blackburn C: Respiratory arrest after epidural sufentanil. Anaesthesia 40:665, 1985
5. Brahams D: Death of a patient participating in a trial of oral morphine for relief of postoperative pain. Lancet 1:1083, 1984
6. Brockway MS, Noble DW, Sharwood-Smith GH, et al: Profound respiratory depression after extradural fentanyl. Br J Anaesth 64:243, 1990

7. Bromage PR, Camporesi EM, Durant PAC, et al: Nonrespiratory side-effects of epidural morphine. Anesth Analg 61:490, 1982
8. Brown JH: Atropine, scopolamine, and related antimuscarinic drugs. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, p 156
9. Catley DM, Thornton C, Jordan C, et al: Pronounced episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. Anesthesiology 63:20, 1985
10. Chestnut DH, Owen CL, Bates JN, et al: Continuous infusion epidural analgesia during labor: A randomized, double-blind comparison of 0.0625% bupivicaine/0.0002% fentanyl versus 0.125% bupivicaine. Anesthesiology 68:754, 1988
11. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. Anesthesiology 61:276, 1984
12. Covino BG: Interpleural regional analgesia. Anesth Analg 67:427, 1988
13. Crone LL, Conly JM, Storgard C, et al: Herpes labialis in parturients receiving epidural morphine following cesarean section. Anesthesiology 73:208, 1990
14. Dahl JB, Christiansen CL, Daugaard JJ, et al: Continuous blockade of the lumbar plexus after knee surgery-postoperative analgesia and bupivacaine plasma concentrations. Anaesthesia 43:1015, 1988
15. Dahl JB, Jacobsen JB: Accidental epidural narcotic overdose. Anesth Analg 70:321, 1990
16. Daley DM, Sandler AN, Turner KE, et al: A comparison of epidural and intramuscular morphine in patients following cesarean section. Anesthesiology 72:289, 1990
17. Drenger B, Magora F: Urodynamic studies after intrathecal fentanyl and buprenorphine in the dog. Anesth Analg 69:348, 1989
18. Durant PAC, Yaksh TL: Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats. Anesthesiology 68:325, 1988
19. Duthie DJR, Nimmo WS: Adverse effects of opioid analgesic drugs. Br J Anaesth 19:61, 1987
20. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. Anesthesiology 68:444, 1988
21. Ellis DJ, Millar WL, Reisner LS: A randomized double-blind study of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology 72:981, 1990
22. Etches RC, Sandler AN, Daley DM: Respiratory depression and spinal opioids. Can J Anaesth 36:165, 1989
23. Evron S, Magora F, Sadovsky E: Prevention of urinary retention with phenoxybenzamine during epidural morphine. Br Med J 288:190, 1984
24. Farrar DJ, Osborne JL: The use of bromocriptine in the treatment of the unstable bladder. Br J Urol 48:235, 1976
25. Ferrante FM, Covino BG: Patient-controlled analgesia: A historical perspective. *In* Ferrante FM, Ostheimer GW, Covino BG (eds): Patient-Controlled Analgesia. Chicago, Year Book Medical, 1990, p 3
26. Garrison JC: Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, p 581
27. Gieraerts R, Navalgund A, Vaes L, et al: Increased incidence of itching and herpes simplex in patients given epidural morphine after cesarean section. Anesth Analg 66:1321, 1987
28. Gillies GWA, Kenny GNC, Bullingham RES, et al: The morphine sparing effect of ketorolac tromethamine. Anaesthesia 42:727, 1987
29. Gowan JD, Hurtig JB, Fraser RA, et al: Naloxone infusion after prophylactic epidural morphine: Effects on incidence of postoperative side-effects and quality of analgesia. Can J Anaesth 35:143, 1988
30. Harrison DM, Sinatra R, Morgese L, et al: Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. Anesthesiology 68:454, 1988
31. Hoffman BB, Lefkowitz RJ: Adrenergic receptor antagonists. *In* Gilman AG, Rall TW,

Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, pp 225–228

32. Jaffe JH, Martin WR: Opioid analgesics and antagonists. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, p 495
33. Jaffe JH, Martin WR: Opioid analgesics and antagonists. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, pp 493, 502
34. Kirson LE, Goldman JM, Slover RB: Low-dose intrathecal morphine for postoperative pain control in patients undergoing transurethral resection of the prostate. Anesthesiology 71:192, 1989
35. Kopacz DJ, Slover RB: Accidental epidural cephazolin injection: Safeguards for patient-controlled analgesia. Anesthesiology 72:944, 1990
36. Kotelko DM, Rottman RL, Wright WC, et al: Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. Anesthesiology 71:675, 1989
37. Kreitzer JM, Kirschenbaum LP, Eisenkraft JB: Safety of PCA devices. Anesthesiology 70:881, 1989
38. Lanz E, Kehrberger E, Theiss D: Epidural morphine: A clinical double blind study of dosage. Anesth Analg 64:786, 1985
39. Loper KA, Ready LB, Dorman BH: Prophylactic transdermal scopolamine patches reduce nausea in postoperative patients receiving epidural morphine. Anesth Analg 68:144, 1989
40. Loper KA, Ready LB, Downey M, et al: Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 70:72, 1990
41. Loper KA, Ready LB, Nessley M, et al: Epidural morphine provides greater pain relief than patient-controlled intravenous morphine following cholecystectomy. Anesth Analg 69:826, 1989
42. Loper KA, Ready LB: Epidural morphine after anterior cruciate ligament repair: A comparison with patient-controlled intravenous morphine. Anesth Analg 68:350, 1989
43. Lysak SZ, Eisenach JC, Dobson CE: Patient-controlled epidural analgesia during labor: A comparison of three solutions with a continuous infusion control. Anesthesiology 72:44, 1990
44. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiology 74:581, 1991
45. Miller RR: Analgesics. *In* Miller RR, Greenblatt DJ (eds): Drug Effects in Hospitalized Patients. New York, Wiley & Sons, 1976, p 151
46. Moffat AC, Kenny GNC, Prentice JW: Postoperative nefopam and diclofenac. Anaesthesia 45:402, 1990
47. Notcutt WG, Morgan RJM: Introducing patient-controlled analgesia for postoperative pain control into a district general. Anaesthesia 45:401, 1990
48. Owen H, Plummer JL, Armstrong LE, et al: Variables in patient-controlled analgesia: 1. Bolus size. Anaesthesia 44:7, 1989
49. Palazzo MGA, Strunin L: Anaesthesia and emesis. Can Anaesth Soc J 31:178, 1984
50. Penning JP, Samson B, Baxter AD: Reversal of epidural morphine-induced respiratory depression and pruritis with nalbuphine. Can J Anaesth 35:599, 1988
51. Pflug AE, Murphy TM, Butler SH, et al: The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8, 1974
52. Raj PP, Knarr D, Vigdorth E, et al: Comparative study of continuous epidural infusions versus systemic analgesics for postoperative pain relief. Anesthesiology 63:A238, 1985
53. Rapp SE, Ready LB, Greer BE: Postoperative pain management in gynecologic patients utilizing epidural opiate analgesia and patient-controlled analgesia. Gynecol Oncol 35:341, 1989
54. Rawal N, Arner S, Gustafsson LL, et al: Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 59:791, 1987
55. Rawal N, Mollefors K, Axelsson K, et al: An experimental study of urodynamic effects of epidural morphine and naloxone reversal. Anesth Analg 62:641, 1983

56. Rawal N, Sjostrand U, Christofferson E, et al: Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: Influence on postoperative ambulation and pulmonary function. Anesth Analg 63:583, 1984
57. Rawal N: Adverse effects of spinal opioids in acute pain and their management. *In* Rawal N, Coombs DW (eds): Spinal Narcotics. Norwell, MA, Kluwer Academic Publishers, 1990, p 77
58. Renaud B, Brichant JF, Clergue F, et al: Ventilatory effects of continuous epidural infusion of fentanyl. Anesth Analg 67:971, 1988
59. Ross EL, Perumbeti P: PCA: Is it cost effective when used for postoperative pain management? Anesthesiology 69:A710, 1988
60. Segstro R, Morley-Forster PK, Lu G: The efficacy of indomethacin as a postoperative analgesic following total hip arthroplasty. Can J Anaesth 37:S41, 1990
61. Sinatra R, Chung KS, Silverman DG, et al: An evaluation of morphine and oxymorphone administered via patient-controlled analgesia (PCA) or PCA plus basal infusion in postcesarean delivery patients. Anesthesiology 71:502, 1989
62. Steinstra R, van Poorten F: Immediate respiratory arrest after caudal epidural sufentanil. Anesthesiology 71:993, 1989
63. Stenseth R, Sellevold O, Breivik H: Epidural morphine for postoperative pain: Experience with 1085 patients. Acta Anaesthesiol Scand 29:148, 1985
64. Taylor P: Cholinergic agonists. *In* Gilman AG, Rall TW, Nies AS, et al (eds): The Pharmacologic Basis of Therapeutics, ed 8. New York, Pergamon Press, 1990, p 127
65. Tessler MJ, White I, Naugler-Colville MA, et al: Inadvertent epidural administration of potassium chloride. A case report. Can J Anaesth 35:631, 1988
66. Thomas DW, Owen H: Patient-controlled analgesia—The need for caution. Anaesthesia 43:770, 1988
67. Torrens M: Human physiology. *In* Torrens M, Morrison JFB (eds): The Physiology of the Lower Urinary Tract. Frome, Springer-Verlag, 1987, p 333
68. Tyler DC, Krane EJ: Epidural opioids in children. J Pediatr Surg 24:469, 1989
69. Walts LF, Kaufman RD, Moreland JR, et al: Total hip arthroplasty: An investigation of factors related to postoperative urinary retention. Clin Orthop 194:280, 1985
70. Wasylak TJ, Abbott FV, English MJM, et al: Reduction of postoperative morbidity following patient-controlled morphine. Can J Anaesth 37:726, 1990
71. White PF: Mishaps with patient-controlled analgesia. Anesthesiology 66:81, 1987
72. Whiting WC, Sandler AN, Lau LC, et al: Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. Anaesthesiology 69:36, 1988
73. Yaksh TL, Noueihed R: The physiology and pharmacology of spinal opiates. Ann Rev Pharmacol Toxicol 25:433, 1985
74. Yeager MP, Glass DD, Neff RK, et al: Epidural anaesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987
75. Zacharias M, Pfeifer MV, Herbison P: Comparison of two methods of intravenous administration of morphine for postoperative pain relief. Anaesth Intensive Care 18:205, 1990

Address reprint requests to

Richard C. Etches, MD
Department of Anesthesia
University of Alberta Hospitals
8440-112 Street
Edmonton, Alberta
Canada T6G 2B7

NURSING ASPECTS OF ACUTE PAIN MANAGEMENT

Lorie Wild, RN, MN

Clinical approaches to acute pain management have changed over the past decade. New pain management modalities such as epidural analgesia and patient-controlled analgesia (PCA) are now routinely available in many clinical settings. The benefits of these new modalities have been well described in both the medical and nursing literature.[2, 3, 11, 12, 18, 23] In addition to new modalities of pain management, the provision of the service of acute pain management has also changed. In many hospital settings, postoperative pain management is managed by an anesthesiology-based acute pain service (APS).[17, 20, 21] Also, nurses are assuming greater responsibility in ensuring optimum pain control for their patients.[4, 5, 15, 22] The result of increasing interest, specialization, and treatment options in acute pain management is improved patient outcomes.[8, 11, 13, 19, 24, 25] The purpose of this article is to explore and describe the role of nursing in acute pain management, both at the bedside and within an APS.

THE TEAM APPROACH TO PAIN MANAGEMENT

For most acute care settings, establishing an APS requires the interest and expertise of several disciplines. The acute pain management team usually incorporates anesthesiologists and nurses, as well as pharmacists, psychologists, and other medical or surgical specialists.[9, 20] This team approach to pain management can prove beneficial to both patients and staff. An APS is comprised of professionals with expertise

---

From the Department of Anesthesiology, University of Washington Medical Center, Seattle, Washington

in the assessment and treatment of acute pain. The approach to pain management is comprehensive due in part to the individual expertise of each of the APS members. The end result of this expertise and experience is an individualized pain management plan for each patient.

Although an APS can benefit patients, they do not provide care in isolation. Members of the APS work not only with patients, but also with the nurses and the primary physician. Thus, collaborative skills are essential. A model of care provided by the APS is shown in Figure 1. Every person identified in the model must interface with the others listed; when communication is strong among them, positive patient outcomes result.

THE ROLE OF THE PRIMARY NURSE

Pain management is within the purview of nursing practice. Nursing is defined as ". . . the diagnosis and treatment of human responses to actual or potential health problems."[1] Certainly, pain is one of the most profound responses to a health problem and often the chief reason individuals seek medical care. The primary care nurse (PCN) assesses the patient's pain, plans for and provides pain-relieving interventions, and evaluates the results of those interventions.

Because the PCN is at the bedside, he or she is at the forefront of patient care and is an essential collaborator with the APS. The PCN is also the primary interface between the patient, the surgeon or other primary physician, and the APS. The PCN can contribute valuable information about the patient and his or her situation that may

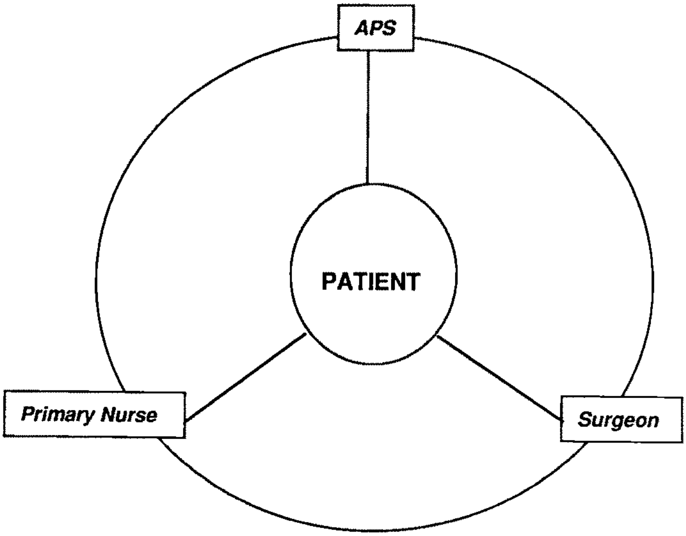


Figure 1. Acute pain service model for care.

significantly affect proposed treatment plans by the APS. Communicating treatment plans to the PCN also helps ensure that treatment plans, especially complex plans, will be carried out as proposed. The PCN can also help in translating or reinforcing explanations of the treatment plan to the patient and others.

In most clinical settings, the PCN is responsible for administering the pain management plan, monitoring its effectiveness, and communicating with the APS regarding any complications or need for changes. The PCN is often the one who titrates the therapy or drug to obtain the desired analgesic response. This titration could range from administration of an intravenous or epidural opioid, to setting up or changing dosage parameters on a PCA device, to applying a transcutaneous electrical nerve stimulator. The scope of nursing practice with respect to specific procedures may vary from hospital to hospital.

THE ROLE OF THE CLINICAL NURSE SPECIALIST

In many settings, a clinical nurse specialist (CNS) is an integral member of the APS.[5, 9, 20, 21] The American Nurses' Association defines a CNS as ". . . a nurse who, through study and supervised practice at the graduate level (master's or doctorate), has become expert in a defined area of knowledge and practice in a selected clinical area of nursing."[1] The application of the CNS role may vary both among and within clinical settings, although the defining characteristics of the role remain constant (Fig. 2). The primary characteristic of the role of the CNS is its focus on clinical practice and the improvement of patient care.[10] In addition to the role of expert clinical practice are the roles of consultation, education, and research.

The skills and competencies of the CNS can be a valuable asset to the APS, especially during its start-up phase. The CNS is skilled as a change agent. The very nature of the CNS role is to examine current practice, recommend changes where indicated, and implement new or altered practice. As pain management undergoes rapid change, the CNS facilitates its transition into daily practice by nurses and other health care professionals. The CNS is able to explore creative methods to introduce new techniques or services such as an APS.

Another skill germane to the CNS role is that of collaborator.[10] The CNS has well-developed communication and negotiating skills, which not only benefit the APS, but also benefit other nurses, physicians, and ancillary departments. The CNS is able to represent nursing practice to physicians and likewise represent medical practice to nurses.[9] Again, the collaboration among the various parties involved with pain management ultimately benefits patients and their care.

As a clinical leader, the CNS is a clinical and systems problem solver or troubleshooter.[10] He or she helps establish clinical priorities that relate to the care of the patient experiencing acute pain. These priorities may relate to the care of a specific patient or groups of

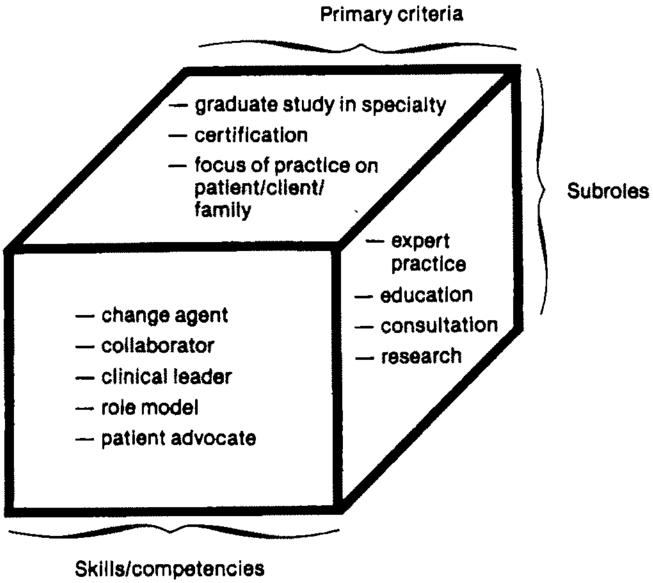


Figure 2. Defining characteristics of the CNS role. (*From* Hamric AB: History and overview of the CNS role. *In* Hamric AB, Spross JA, (eds): The Clinical Nurse Specialist in Theory and Practice. Philadelphia, WB Saunders, 1989, p 8; with permission.)

patients. The CNS can assist the PCN or the APS to maneuver through the complexities of "the system" and get it to respond. This type of systems savvy can be a valuable contribution of the CNS.

The CNS also serves as a professional role model to staff nurses.[10] Through his or her clinical practice, the CNS for pain management can exemplify the priorities associated with promoting comfort in acutely ill patients.

Finally, the CNS possesses skills as a patient advocate.[10] Throughout all of what a CNS does is the goal of improving patient care and outcomes. Whether working with the PCN, the APS, or other departments, the systems savvy a CNS possesses ultimately assists patients in getting what they need to both enhance and hasten their recovery. Fenton[7] has succinctly summarized the advocacy role of the CNS: "The CNS serves as a path finder for those patients whose needs get lost in the system."

CONSULTATION

As a clinical expert, the CNS consults with nurses, patients, physicians, families, other departments, and institutions regarding acute pain management. CNS consultation occurs in a variety of ways. Daily APS rounds not only provide an opportunity for contact with patients, but also with other health care professionals. The CNS is often the link for continuity of patient care provided by the APS, especially in the environment of the teaching hospital. While house staff and attending physician coverage may change periodically, the CNS can lend an element of constancy with regard to patient care.

The CNS also consults directly with patients. The CNS can assess patients who have complex pain management needs and suggest an assortment of analgesic strategies for patients to consider. The pain management CNS may also participate in patient care conferences where multidisciplinary planning for specific patient care needs are addressed.

Consultation with the PCN by the CNS may address specific concerns or problems encountered with a patient's pain management plan. This consultation may range from troubleshooting a PCA pump to coordinating a dosing schedule to maximize patient comfort during intermittent procedures such as wound care.

At other times, the CNS consults with small groups of nurses or other interdisciplinary groups who have come together to solve problems or develop a new idea for pain management.

Administrative consultation may involve activities such as quality assurance, protocol development, and follow-up on risk management issues related to acute pain management. The pain management CNS is often in a position to consult and collaborate with other departments such as pharmacy and materials management for the purpose of program planning. Consultation with the pharmacy may involve drug supply, new trends in APS practice, or developing preprinted, standard orders for new therapies. Regular and formalized collaboration with the pharmacy helps ensure that patients and nurses get the medications they need safely and in a timely manner. Work with the materials management department usually revolves around equipment acquisition, availability, and troubleshooting. The CNS may be responsible for developing an evaluation plan for new patient care equipment that is used by the APS. Again, the CNS's work with the materials management department ultimately benefits patients by having safe, efficient, and usable equipment readily available for their use.

EDUCATION

Another key role the CNS has within a pain management program is that of education. The pain management CNS may be responsible for the education regarding the APS, as well as other generic pain management issues. The CNS may coordinate and provide education on pain management topics for staff nurses, anesthesiology residents and fellows, house staff from other medical services, and other interested departments.

The education provided by the CNS may be either formal or, in many cases, informal. The CNS develops and presents many formal educational programs for staff. Formalized educational inservices, classes, or workshops address a variety of topics related to pain management. Teaching staff about new modalities of pain management is a principal thrust.

The CNS is an educational resource to search for new or additional references for staff to facilitate their learning about pain management techniques.

For most CNSs, however, the majority of education that he or she provides is informal and takes place on the clinical unit. Typically, teaching is specific to a particular patient problem or need. The CNS is in a position to give information and share his or her expertise at the point of practice.

In many settings, the CNS is responsible for orienting new nurses to the pain management modalities used in their setting or by the APS. While orientation of new employees regarding pain management by the pain management CNS can be a time-consuming endeavor, it is beneficial in the long-term because new nurses are introduced to a philosophy of pain management in addition to equipment and techniques.

Finally, the CNS provides patient education regarding pain management. Patient education can also be both formal or informal. Formalized preoperative education for patients may be conducted by the CNS. But as with nursing education, the majority of patient education takes place at the bedside. The CNS is in a position to teach patients how they can effectively manage their pain whether they are using a PCA device or oral analgesics.

RESEARCH

Because the CNS is prepared at the graduate level, he or she has training in the conduct and application of research.[1, 16] Bringing research to the bedside is a critical function of the CNS. Within the research role, the CNS reviews, interprets, and communicates current research findings in the area of pain management to nursing staff. In addition, the CNS uses research findings when working with patients and nurses, as well as when developing or revising procedures and protocols for pain management. Fostering a pain management practice based in research is imperative.

The CNS often serves as a liaison between nursing staff and the APS regarding research protocols. Informing nurses about upcoming studies in which they or their patients will be enrolled helps elicit their support of the project. When staff understand and support APS research, studies can progress more efficiently. The CNS can assist the PCN in integrating a research protocol into standard nursing care.

From another perspective, the CNS collaborates with APS investigators in devising research protocols that are realistic with regard to established patient or nursing routines. The CNS may also be involved in other components of a research study such as enrolling subjects, data collection, and disseminating findings. In addition to collaborating with other APS researchers, the CNS may initiate his or her own research associated with APS clinical activities.

DEVELOPING THE NURSING ROLE

As discussed previously, the PCN is the crucial link to optimal patient care, especially regarding pain management. In light of this, support for the PCN is of paramount importance. Support can take many forms: prompt response on the part of the APS to address questions raised by the PCN about patients' pain management needs, providing user-friendly, reliable equipment, and clear, practical documentation requirements for pain assessment and interventions to name just a few.

The importance of comprehensive educational programs to support the PCN should not be underestimated. Basic nursing education introduces the professional nurse to theory and concepts related to pain management. Unfortunately, there is often a gap between the introduction of new pain management techniques into the clinical setting and their incorporation into nursing curriculae. It is hoped that as the relationship of new pain management techniques with improved patient outcomes strengthens through research findings, this information will be incorporated into nursing curriculae.[5]

At this time, much of the education regarding specific modalities for pain management occurs in the clinical setting or through continuing education conferences and workshops. In today's clinical setting, PCNs must keep abreast of numerous new drugs and modalities of pain management. Learning to operate new equipment and understand new drugs places additional demands on the time of a busy PCN, but ultimately benefits patients as they become skilled in their use. Educational programs should address the use of the new modality, pertinent background or theoretical information, and the nursing management of patients who are using the new drug or modality. Safety considerations are critical in introductory and advanced education programs and may include troubleshooting aspects, how to detect problems or complications associated with the therapy quickly, as well as how to respond to problems if they occur.

Formalized educational programs often employ a "train-the-trainer" approach to new pain management modalities. In this approach, a few, key nurses from each patient care unit are trained in a new technique and are then available as on-unit resources for other staff as they begin to learn the technique. Similar to train-the-trainer educational programs are those that concentrate on advanced skills to develop nurses as unit-based experts in an area of pain management such as epidural analgesia or PCA. Many hospitals set up an in-house certification program when training staff nurses on new modalities or equipment. Clearly, formalized nursing education can occur in a variety of ways. In any case, setting up educational offerings, either prior to or simultaneous with the initiation of a new pain management program is not just desirable, but is essential to its successful implementation.

Beyond the initial education of nurses regarding pain management modalities is the ongoing need for accessible, updated information. Unit-based inservices are often scheduled as updates occur. Creating resource files or notebooks on pain management also can be an effective means of conveying new information to nursing staff. Other informal methods of teaching may include newsletters, fliers, or written reminders. In our hospital, we have found that poster presentations, which travel from unit to unit, depicting the salient points of a various pain management topics are a useful and efficient method of communicating new information.

Finally, the orientation of newly hired nurses is needed. Spending time in orientation learning about pain management (and the APS, if the hospital features this service) introduces these new nurses to a philosophy of pain management in addition to equipment and techniques.

SUMMARY

The role of nursing in the management of acute pain is expanding. Historically, just as physicians have been prone to underprescribe opioid analgesics for their patients, nurses have been reluctant to administer those prescribed doses.[6, 14] As research begins to demonstrate the benefits of early and aggressive management of acute postoperative pain, care givers, both medical and nursing, have a growing responsibility to respond by planning and implementing comprehensive pain management programs.[24] Fundamental to the implementation and success of these programs is the education and support for the PCN, who is at the bedside. To this end, the role of the CNS within a developed APS is beneficial for other nurses, physicians, and most of all patients. The prelude for optimal pain management is practitioners skilled in the assessment and treatment of patients experiencing acute pain. As physicians and nurses work collaboratively in an effort to achieve the goal of optimal pain management, patients are sure to benefit.

References

1. American Nurses' Association: Nursing: A social policy statement. Kansas City, MO, American Nurses' Association, 1980
2. Bennett R: Postoperative pulmonary function with patient-controlled analgesia. Anesth Analg 61:171, 1982
3. Bollish S: Efficacy of patient-controlled versus conventional analgesia for postoperative pain. Clin Pharm 4:48–52, 1985
4. Champman PJ, Ganendran A, Scott RJ, et al: Attitudes and knowledge of nursing staff in relation to management of postoperative pain. Aust NZ J Surg 57:447–450, 1987

5. Clark LA: The nurse: An important player in acute pain management. Analgesia 2:7–9, 1991
6. Cohen FL: Postsurgical pain relief: Status and nurses' medication choices. Pain 9:269–274, 1980
7. Fenton MV: Identifying competencies of clinical nurse specialists. J Nurs Admin 15:31–37, 1985
8. Finley RJ, Keeri-Szanto M, Boyd D: New analgesic agents and techniques shorten postoperative hospital stay. Pain 2:S397, 1984
9. Hammonds WD, Reed B, Kelly P, et al: Pain management team. Anesth Report 2:148–154, 1990
10. Hamric AB: History and overview of the CNS role. *In* Hamric AB, Spross JA: The Clinical Nurse Specialist in Theory and Practice. Philadelphia, Saunders, 1989, pp 3–18
11. Jackson D: A study of pain management: patient controlled analgesia versus intramuscular analgesia. Mich J Intravenous Ther 12:42–51, 1989
12. Jones L, Neiswender JA, Perkins M: PCA: Patient satisfaction, nursing satisfaction, and cost-effectiveness. Nurs Manag 20:16–17, 1989
13. Lange MP, Dahn MS, Jacobs LA: Patient-controlled analgesia versus intermittent analgesia dosing. Heart Lung 17:495–498, 1988
14. Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 78:173–181, 1973
15. McCaffery M, Beebe A: Pain: Clinical Manual for Nursing Practice. St. Louis, C.V. Mosby, 1989
16. McGuire DB, Harwood KV: The CNS as researcher. *In* Hamric AB, Spross JA: The Clinical Nurse Specialist in Theory and Practice. Philadelphia, WB Saunders, 1989, pp 169–203
17. Ramsey DH: Perioperative pain: Establishing an analgesia service. *In* Brown DL: Problems in Anesthesia—Perioperative Analgesia. Philadelphia, JB Lippincott, 1988, pp 321–326
18. Rao MK, Balcueva EP, Thiem C, et al: Evaluation of demand analgesia in a community hospital. Res Staff Phys 32:26–30, 1986
19. Ready LB: Patient-controlled analgesia—Does it provide more than comfort? 37:719–721, 1990
20. Ready LB, Oden R, Chadwick HS, et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100–106, 1988
21. Ready LB, Wild LM: Organization of an acute pain service: Training and manpower. Anesthesiol Clin North Am 7:229–239, 1989
22. Rogers A: The nurse as acute pain specialist. Pain Management Mar/Apr, 73–77, 1988
23. Ross EL, Perumbeti P: PCA: Is it cost effective when used for postoperative pain management? Anesthesiology 69:A710, 1988
24. Wasylak TJ, Abbott FV, English MJM, et al: Reduction of postoperative morbidity following patient-controlled analgesia. Can J Anaesth 37:726–731, 1990
25. Yeager MP, Glass DD, Neff RK, et al: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729–736, 1987

Address reprint requests to

Lorie Wild, RN, MN
Department of Anesthesiology
University of Washington Medical Center
1959 NE Pacific RN-10
Seattle, Washington 98195

INDEX

Note: Page numbers of article titles are in **boldface** type.

Acetaminophen, for pediatric analgesia, 367
Acute pain control. See *Pain control, acute.*
Afferent pathways, 221–223
Agonist-antagonist narcotics, 383. See also α_2-*Agonists.*
Alfentanil, for epidural postoperative analgesia, 328
α_2-Agonists, 312–315
  clonidine, 313–315, 330–332, 406
  dexmedetomidine, 315
  for epidural postoperative analgesia, 330–332
  for preventing urinary retention, 423
Analgesic agents, systemic. See *Systemic analgesic agents.*
Analog Chromatic Continuous Scale, 360
Anti-inflammatory agents, in critically ill patients, 398
  nonsteroidal, for pediatric analgesia, 367–368
  prevention of secondary hyperalgesia, 214

Barbiturates, for obstetric pain management, 384
Benzodiazepines, 384, 407
Brachial plexus block, 350–352, 369, 401
Bradykinin, pain sensitization caused by, 251, 253
Bupivacaine, combined with morphine, 329–330
  continuous infusion of, 402
  in obstetric pain management, 387

C-fiber neuropeptides, in central sensitization, 219–220, 259–260
  in peripheral sensitization, 213–214
C-*fos* proto-oncogene, and central sensitization, 262–263
Calcitonin gene-related peptide, central sensitization and, 259–260
Calcium, intracellular, and central sensitization, 260, 262
Capsaicin, 315–316
Cellular messengers, and central sensitization, 260–262
Central sensitization, 219–221, 254–263
  causes of, 219–220
  of dorsal horn neurons, 255–263
    alterations in flexion reflexes, 257
    animal models of persistent pain, 257–259
    cellular messengers and, 260–262
    molecular events and, 262–263
    neurochemical mediators of sensitization, 259–260
    receptive field expansion, 255–257
  prevention of, 220–221
  as a result of tissue injury, 254–263
Cervical plexus block, in infants and children, 368
Chloroprocaine, for obstetric pain management, 387–388
Clonidine, 313–315, 330–332, 406
Codeine, for pediatric analgesia, 365–366
Convulsions, caused by regional analgesia, 390
Critically ill patients, pain control in, assessing the patient's pain, 397–398
  complications, 409–410
  hemodynamic stability, 410–411
  length of hospital stay, 411
  local anesthetic techniques, 399–401
  nonsteroidal anti-inflammatory agents, 398
  pain-related behavior, 395–396
  regional blocks, 399–401
  spinal analgesia, 401–406

Critically ill patients *(Continued)*
    epidural or subarachnoid blocks, 401–406
    transcutaneous electrical nerve stimulation, 401
  systemic analgesia, 407–411
    opioids, 407–409
    sedation, 407

Descriptor Differential Scale, 239, 240
Dexmedetomidine, 315
Dezocine, 299–307
  abuse potential, 300–302
  adverse effects, 307
  analgesic activity, 302–303
  cardiovascular effects, 305
  clinical trials, 305–307
  increased analgesia following morphine administration, 304–305
  pharmacokinetics, 302
  respiratory effects, 303–305
Dorsal horn neurons, 217–221
  central sensitization of, 219–221
    alterations in flexion reflexes, 257
    animal models of persistent pain, 257–259
    causes of, 219–220
    cellular messengers and, 260–262
    clinical significance, 220–221
    molecular events and, 262–263
    neurochemical mediators of sensitization, 259–260
    receptive field expansion, 255–257
  classes of neurons responsive to nociceptive stimuli, 217–218
  organization of, 217–218
  spinal afferent processing, 218–219
  wide dynamic range (WDR) neurons, 218–219

EMLA cream, 361, 363
Epidural analgesia, in critically ill patients, 402–406
    catheter placement, 402
    combined local anesthetic-opioid infusions, 406
    continuous local anesthetic, 402
    continuous opioid infusions, 406
    opioids alone, 403–406
    other agents, 406
  in infants and children, 371–372
  for obstetric pain management, 385–389
    choice of local anesthetic, 387–388
    contraindications, 389
    management, 388–389
  postoperative, **321–337**
    alfentanil, 328
    α_2-agonists, 330–332
    fentanyl, 326–327
    local anesthetics, 321–324
    meperidine, 325–326
    morphine, 324–325
    narcotic agonist-antagonists, 328–329
    opioid-local anesthetic combinations, 329–332
    opioids, 324–328
    sufentanil, 327–328
Epinephrine, effect on local anesthetics, 349
Eutectic mixture of local anesthetic (EMLA) cream, 361, 363

Fentanyl. See also *Transdermal therapeutic system (TTS)-fentanyl.*
  for epidural postoperative analgesia, 326–327
  for obstetric pain management, 382
  for pediatric analgesia, 364–365
Flexion reflexes, alterations in, 257

Glutamate, and central sensitization, 259–260

Hemodynamic stability, after epidural opioids, 410–411
Histamine, as cause of pain sensitization, 251, 253, 254
Hyperalgesia, secondary, caused by inflammatory peptides, 214
  following tissue injury, 248
  preventing, 214
  spread by central sensitization, 254–255
Hypotension, secondary to analgesia, 390, 402, 404

Ilioinguinal/iliohypogastric block, 369–370
Indomethacin, for pediatric analgesia, 367
Infants and Children, pain control in. See *Pediatric pain control.*
Inflammation, 248
  and pain sensitization, 251–254
Inhalational analgesia, for obstetric pain management, 381–382
Intensive care patients. See *Critically ill patients, pain control in.*
Intercostal nerve blocks, 344–346, 369, 399–400

Interpleural analgesia, in critically ill patients, 400–401
  in infants and children, 368–369
  regional block techniques, 346–350
Intravenous regional block, in infants and children, 369

Ketamine, for obstetric pain management, 384
Ketorolac, 307–312, 367–368

Lidocaine, for obstetric pain management, 387
Local anesthetics, in critically ill patients, 399–401
  effect of epinephrine, 349
  for epidural analgesia, 321–324
    combined with opioids, 329–332, 406
  hyperalgesia delayed by, 252
  in infants and children, 368
  for wound infiltration, 340–342, 399
Local nerve blocks. See *Regional and local blocks.*
Lumbar plexus block, in infants and children, 370

McGill Pain Questionnaire, 232–239
McGill Pain Questionnaire, short-form, 239, 240, 398
Measurement of pain, **229–246**
  Analog Chromatic Continuous Scale, 360
  behavioral measures, 241–242
  Children's Comprehensive Pain Questionnaire, 360
  Children's Hospital of Eastern Ontario Pain Scale, 360
  Descriptor Differential Scale, 239, 240
  dimensions of pain experience, 229–230
  language descriptive of pain, 230–231
  McGill Pain Questionnaire, 232–239
  physiologic measures, 242
  short-form McGill Pain Questionnaire, 239, 240, 398
  visual analogue scales (VAS), 231–232, 397
Meperidine, for epidural postoperative analgesia, 325–326
  for obstetric pain management, 382
Methadone, for pediatric analgesia, 365
Morphine, and enhancement of analgesic effects of dezocine, 304–305
  for epidural postoperative analgesia, 324–325
  for obstetric pain management, 382, 391–392
  for pediatric analgesia, 364

Naloxone, for reversing side effects of opioids, 419, 420, 421, 424
Narcotic agonist-antagonists, for epidural postoperative analgesia, 328–329
Narcotics. See *Opioids.*
Nausea and vomiting, secondary to opioids, 418–420
Neurologic injury, caused by regional analgesia, 390–391
Neuropeptides. See *C-fiber neuropeptides.*
Nitrous oxide, in infants and children, 362
Nociception, defined, 211, 396
Nociceptors, characteristics of, 212
  mechanonociceptors, 212–213
  noncutaneous nociceptors, 216
  peripheral receptors, 211–216
  polymodal nociceptors, 213
  sensitization after tissue injury, 248–250
Noncutaneous nociceptors, 216
Nursing aspects of acute pain management, **435–443**
  developing the nursing role, 441–442
  education for pain management, 427–428
  primary care nurses, 433–437
  role of nurse specialist, 428–429, 437–441
  team approach to pain management, 435–436

Obstetric pain management, **379–394**
  complications of regional analgesia, 390–391
  inhalational analgesia, 381–382
  ketamine, 384
  labor pain pathways, 380
  lumbar epidural analgesia, 385–389
  narcotics, 383
  paracervical block, 389
  psychoprophylaxis, 380
  pudendal block, 390
  regional analgesia, 384–391
  sedatives and tranquilizers, 384
  spinal narcotics, 391–392
  systemic medication, 382–384
  transcutaneous electrical nerve stimulation, 380–381

- Opioids. See also *Patient-controlled analgesia (PCA); Transdermal therapeutic system (TTS)-fentanyl.*
  - administration of, continuous intravenous infusions, 289, 407–408
    - oral mucosal administration, 271–273
    - rectal administration, 273–274
    - transdermal administration, 274–284
  - complications of, **417–433**
    - due to equipment failure, 426–427
    - hospital acute pain service for prevention of, 427–429
    - nausea and vomiting, 418–420
    - opioid-sparing strategies, 429
    - prevention of, 427–429
    - pruritus, 420–421
    - respiratory depression, 424–426
    - urinary retention, 422–424
  - epidural, in critically ill patients, combined local anesthetic-opioid infusions, 406
    - continuous infusion, 406
    - intermittent doses, 403–406
    - side effects, 404–406
  - for epidural postoperative analgesia, 324–328
    - alfentanil, 328
    - combined with local anesthetics, 329–332
    - fentanyl, 326–327
    - meperidine, 325–326
    - morphine, 324–325
    - sufentanil, 327–328
  - for obstetric pain management, 382
    - agonist-antagonist narcotics, 382
    - epidural administration, 391–392
    - fentanyl, 382
    - meperidine, 382
    - morphine, 382
  - for pediatric analgesia, 364–366
    - codeine, 365–366
    - fentanyl, 364–365
    - methadone, 365
    - morphine, 364
    - sufentanil, 365
  - subarachnoid administration, 401–402
- Opioids of, administration, **271–286**, 407–409
- Oral mucosal administration of opioids, 271–273

- Pain control, acute, administration of opioids for, *271–286*
    - oral mucosal administration, 271–273
    - rectal administration, 273–274
    - transdermal administration, 274–284
  - complications of opioid analgesia, **417–433**
    - misadventure (equipment failure), 426–427
    - prevention of complications, 427–429
    - side effects, 418–426
  - in critically ill patients, **395–415**
    - assessing the patient's pain, 397–398
    - local anesthesia and regional blocks, 399–401
    - nonsteroidal anti-inflammatory agents, 398
    - pain-related behavior, 395–396
    - related to complications, outcome, and length of stay, 409–411
    - spinal anesthesia, 401–406
    - systemic analgesia, 407–411
  - in infants and children, **359–378**
    - acute pain in sickle cell disease, 372
    - nonopioid analgesics, 367
    - nonsteroidal anti-inflammatory drugs, 367–368
    - opioid analgesics, 364–366
    - pain assessment, 359–360
    - pain associated with procedures, 361–363
    - patient-controlled analgesia, 366–367
    - perioperative acute pain, 363–364
    - regional blockade, 368–372
    - treatment, 361–372
  - measurement of pain, **229–246**
    - behavioral measures, 241–242
    - Descriptor Differential Scale, 239, 240
    - dimensions of pain experience, 229–230
    - language descriptive of pain, 230–231
    - McGill Pain Questionnaire, 232–239
    - physiologic measures, 242
    - short-form McGill Pain Questionnaire, 239, 240
    - visual analogue scales (VAS), 231–232
  - new systemic analgesic agents, **299–320**
    - α_2-agonists, 312–315
    - capsaicin, 315–316
    - clonidine, 313–315
    - dexmedetomidine, 315
    - dezocine, 299–307
    - ketorolac, 307–312
  - nursing aspects, **435–443**
    - clinical nurse specialist and, 437–441
    - development of the nursing role, 441–442
    - primary nurse's role, 436–437
    - team approach to pain management, 435–436
  - obstetric pain management, **379–394**
    - inhalational analgesia, 381–382
    - labor pain pathways, 380
    - psychoprophylaxis, 380

    - regional analgesia, 384–391
    - spinal narcotics, 391–392
    - systemic medication, 382–384
    - transcutaneous electrical nerve stimulation, 380–381
  - pain reception and processing, **211–228**
    - afferent pathways, 221–223
    - dorsal horn and afferent processing, 217–221
    - origins of pain, 211
    - peripheral receptors, 211–216
  - patient-controlled analgesia, **287–298**
    - historical perspective, 287–288
    - intravenous patient-controlled analgesia, 291–296
    - traditional analgesic regimes, 288–291
  - physiologic consequences of tissue injury, **247–269**
    - alterations in flexion reflexes, 257
    - animal models of persistent pain, 257–259
    - central effects, 254–263
    - central sensitization, 259–263
    - neurogenic inflammation, 251–254
    - nociceptor sensitization, 248–250
    - pain-producing substances, 250–251
    - peripheral effects, 248–254
    - receptive field expansion, 255–257
    - sensitization of dorsal horn neurons, 255–263
  - postoperative epidural analgesia, **321–337**
    - alfentanil, 328
    - α_2-agonists, 330–332
    - fentanyl, 326–327
    - local anesthetics, 321–324
    - meperidine, 325–326
    - morphine, 324–325
    - narcotic agonist-antagonists, 328–329
    - opioid-local anesthetic combinations, 329–332
    - opioids, 324–328
    - sufentanil, 327–328
  - regional and local blocks, **339–357**
    - brachial plexus block, 350–352
    - future developments, 352
    - intercostal nerve blocks, 344–346
    - interpleural analgesia, 346–350
    - local anesthetic wound infiltration, 340–342
    - peripheral nerve blocks, 342–344
- Paracervical block, 389
- Paravertebral block, 400
- Patient-controlled analgesia (PCA), **287–298**
  - in critically ill patients, 408–409
  - definition of PCA modes and dosing, 291
  - educational and attitudinal problems, 290–291
  - historical perspective, 287–288
  - individual analgesic requirements, 291–294
  - in infants and children, 366–367
  - intravenous patient-controlled analgesia, 291–296
  - minimal effective analgesic concentration (MEAC), 288–289
  - in obstetric pain management, 389
  - PCA paradigm, 288–290
  - pharmacodynamic factors, 292–293
  - pharmacokinetic factors, 292
  - psychologic factors, 293–294
  - safety and problems, 294–296, 409, 426–427
  - traditional analgesic regimens, 288–291
- Pediatric pain control, **359–378**
  - acute pain in sickle cell disease, 372
  - nonopioid analgesics, 367
  - nonsteroidal anti-inflammatory drugs, 367–368
  - opioid analgesics, 364–366
  - oral administration or opioids, 272
  - pain assessment, 359–360
  - pain associated with procedures, 361–363
  - patient-controlled analgesia, 366–367
  - perioperative acute pain, 363–364
  - regional blockade, 368–372
  - treatment, 361–372
- Penile block, in infants and children, 370
- Peripheral nerve blocks, 342–344
- Peripheral receptors, 211–213
- Peripheral sensitization, 213–216, 248–254
  - neurogenic inflammation, 251–254
  - nociceptor sensitization, 248–250
  - pain-producing substances, 250–251
- Persistent pain, animal models of, 257–259
- Phantom limb pain, 257–259
- Phenothiazines, for obstetric pain management, 384
- Phenoxybenzamine, 423
- Physiologic consequences of tissue injury, **247–269**
  - alterations in flexion reflexes, 257
  - animal models of persistent pain, 257–259
  - central effects, 254–263
  - central sensitization, 259–263
  - neurogenic inflammation, 251–254
  - nociceptor sensitization, 248–250
  - pain-producing substances, 250–251
  - peripheral effects, 248–254
  - receptive field expansion, 255–257
  - sensitization of dorsal horn neurons, 255–263

Postdural puncture headache, 391
Potassium, as cause of pain sensitization, 251, 253
Prostaglandins, as cause of pain sensitization, 251, 254
Protein kinases, and central sensitization, 260, 261
Proto-oncogenes, and central sensitization, 262–263
Prutitus, secondary to opioids, 420–421
Pudendal block, for obstetric pain management, 390
Pulmonary function/complications, preventing, 409–410

Receptors. See *Nociceptors; Peripheral receptors.*
Rectal administration of opioids, 273–274
Regional and local blocks, **339–357**
  brachial plexus block, 350–352, 369, 401
  cervical plexus block, 368
  complications, 390–391
  in critically ill patients, 399–401
  epidural, in infants and children, 371–372
  femoral nerve block, 370
  future developments, 352
  ilioinguinal/iliohypogastric block, 369–370
  in infants and children, 368–372
  intercostal nerve blocks, 344–346, 369, 399–400
  interpleural analgesia, 346–350, 368–369, 400–401
  intravenous regional block, 369
  local anesthetic, 340–342, 368, 399
  lumbar epidural analgesia, 385–389
  lumbar plexus block, 370
  for obstetric pain management, 384–391
  paracervical block, 389
  paravertebral block, 400–401
  penile block, 370
  peripheral nerve blocks, 342–344
  principles, 384–385
  pudendal block, 390
  sciatic nerve block, 370
Respiratory effects or depression, secondary to analgesia, clonidine, 314–315
  dezocine, 303–305
  ketorolac, 310
  opioids, 404–406, 424–426
  TTS-fentanyl therapy, 278, 279, 283
Ropivacaine, for obstetric pain management, 387–388

Sciatic nerve block, in infants and children, 370
Second messenger systems, and central sensitization, 260–262
Sedatives, in critically-ill patients, 407
  for obstetric pain management, 384
Sensitization. See *Central sensitization; Peripheral sensitization.*
Serotonin, pain sensitization caused by, 251
Sickle cell disease, acute pain in, 372
Subarachnoid administration, of opioids, 401–402
  of other agents, 406
Substance P, and neural sensitization, 214, 253–254, 259–260
Sufentanil, for epidural postoperative analgesia, 327–328
  for pediatric analgesia, 365
Systemic analgesic agents, **299–320**
  α_2-agonists, 312–315
  capsaicin, 315–316
  clonidine, 313–315
  dexmedetomidine, 315
  dezocine, 299–307
  ketorolac, 307–312
  opioids, 407–409
  sedatives, 407

Third messenger systems, and central sensitization, 262–263
Tissue injury. See *Physiologic consequences of tissue injury.*
Tranquilizers, for obstetric pain management, 384
Transcutaneous electrical nerve stimulation, 380–381, 401
Transdermal therapeutic system (TTS)-fentanyl, 274–284
  advantages and disadvantages, 274–275
  analgesic effects, 277–282
  arterial blood gas measurements during, 280
  comparative studies, 277–279, 282
  pharmacokinetics, 276–277
  respiratory depression, 278, 279, 283
  schematic of membrane permeation system, 275
  side effects, 278–279
  visual analogue scale measurement, 280–281

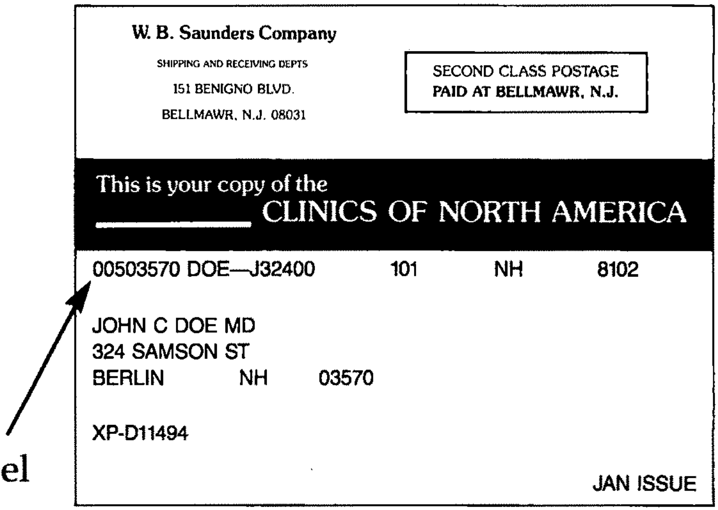
Urinary retention, secondary to opioids, 422–424

VAS. See *visual analogue scales (VAS)*.
Visceral pain, 216
Visual analogue scales (VAS), 231–232, 280–281, 359–360, 397
Wide dynamic range (WDR) neurons, 218–219
Wound infiltration by local anesthetics, 340–342, 399

Changing Your Address?

Make sure your subscription changes too! When you notify us of your new address, you can help make our job easier by including an exact copy of your Clinics label number with your old address (see illustration below.) This number identifies you to our computer system and will speed the processing of your address change. Please be sure this label number accompanies your old address and your corrected address—you can send an old Clinics label with your number on it or just copy it exactly and send it to the address listed below.

We appreciate your help in our attempt to give you continuous coverage. Thank you.



W. B. Saunders Company
SHIPPING AND RECEIVING DEPTS
151 BENIGNO BLVD.
BELLMAWR, N.J. 08031

SECOND CLASS POSTAGE
PAID AT BELLMAWR, N.J.

This is your copy of the
__________ CLINICS OF NORTH AMERICA

00503570 DOE—J32400 101 NH 8102

JOHN C DOE MD
324 SAMSON ST
BERLIN NH 03570

XP-D11494

JAN ISSUE

Your Clinics Label Number

Copy it exactly or send your label
along with your address to:
W.B. Saunders Company, Customer Service
Orlando, FL 32887-4800
Call Toll Free 1-800-654-2452

Please allow four to six weeks for delivery of new subscriptions and for processing address changes.

Order your subscription today. Simply complete and detach this card and drop it in the mail to receive the best clinical information in your field.

YES! Please start my subscription to the Clinics checked below with ☐ the first issue of the calendar year or ☐ current issue, and continue my subscription at the current price until I notify you otherwise. If not completely satisfied with my first issue, I may write "cancel" on the invoice and return it within 30 days at no further obligation.

☐ Bill me ☐ Check enclosed
☐ VISA ☐ MasterCard ☐ AmEx

Card # ____/____/____ exp. ____/____

Signature ____________________

Make checks payable to **W.B. SAUNDERS COMPANY.**
Staple this to your purchase order to expedite delivery.

Please Print:

Name ____________________

Address ____________________

City ____________________

State ____________________ Zip __________

☐ **Anesthesiology**
Quarterly $78
Institutions $98

☐ **Cardiology**
Quarterly $81
Institutions $97

☐ **Chest Medicine**
Quarterly $84
Institutions $100

☐ **Chest Surgery**
Quarterly $79
Institutions $93

☐ **Child & Adolescent Psychiatric**
Quarterly $85
Institutions $99

☐ **Critical Care**
Quarterly $78
Institutions $94

☐ **Dental**
Quarterly $69
Institutions $85

☐ **Dermatologic**
Quarterly $95
Institutions $112

☐ **Emergency Medicine**
Quarterly $78
Institutions $96
☐**Send CME info**

☐ **Endocrinology & Metabolism**
Quarterly $84
Institutions $99

☐ **Gastroenterology**
Quarterly $84
Institutions $99

☐ **Gastrointestinal Endoscopy**
Quarterly $83
Institutions $97

☐ **Geriatric Medicine**
Quarterly $73
Institutions $95

☐ **Hand**
Quarterly $99
Institutions $114

☐ **Hematology/ Oncology**
Bimonthly $93
Institutions $110

☐ **Immunology & Allergy**
Quarterly $74
Institutions $94

☐ **Infectious Disease**
Quarterly $77
Institutions $93
☐**Send CME info**

☐ **Infertility & Reproductive Medicine**
Quarterly $68
Institutions $88

☐ **Laboratory Medicine**
Quarterly $69
Institutions $85

☐ **Medical**
Bimonthly $66
Institutions $85
*Residents $50
☐**Send CME info**

☐ **Neuroimaging**
Quarterly $89
Institutions $105

☐ **Neurologic**
Quarterly $82
Institutions $101

☐ **Neurosurgery**
Quarterly $89
Institutions $113

☐ **Obstetrics & Gynecology**
Quarterly $79
Institutions $100

☐ **Opthalmology**
Quarterly $86
Institutions $113

☐ **Oral & Maxillofacial Surgery**
Quarterly $79
Institutions $96

☐ **Orthopedic**
Quarterly $84
Institutions $102

☐ **Orthopaedic Physical Therapy**
Quarterly $49
Institutions $65

☐ **Otolaryngologic**
Bimonthly $99
Institutions $127
☐**Send CME info**

☐ **Pediatric**
Bimonthly $65
Institutions $83
*Residents $49
☐**Send CME info**

☐ **Perinatology**
Quarterly $69
Institutions $85
☐**Send CME info**

☐ **Physical Medicine & Rehabilitation**
Quarterly $69
Institutions $83

☐ **Plastic Surgery**
Quarterly $110
Institutions $134

☐ **Podiatric Medicine & Surgery**
Quarterly $77
Institutions $95

☐ **Primary Care**
Quarterly $67
Institutions $83
☐**Send CME info**

☐ **Psychiatric**
Quarterly $79
Institutions $98

☐ **Radiologic**
Bimonthly $98
Institutions $114
*Residents $74
☐**Send CME info**

☐ **Rheumatic Disease**
Quarterly $82
Institutions $104

☐ **Sports Medicine**
Quarterly $80
Institutions $97

☐ **Surgical**
Bimonthly $86
Institutions $103
*Residents $65
☐**Send CME info**

☐ **Surgical Oncology**
Quarterly $79
Institutions $91

☐ **Urologic**
Quarterly $86
Institutions $110
☐**Send CME info**

*To receive resident rate, orders must be accompanied by the name of the affiliated institution, dates of residency and signature of residency coordinator on institution letterhead. Orders will be billed at the individual rate until proof of resident status is received.

1992. Offer valid in U.S. only. Prices subject to change without notice.

MO 1671
DO 6126

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 7135 ORLANDO, FL

POSTAGE WILL BE PAID BY ADDRESSEE

PERIODICALS ORDER FULFILLMENT DEPT.
WB SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
6277 SEA HARBOR DR
ORLANDO FL 32821-9816